PATHOGENESIS AND TREATMENT

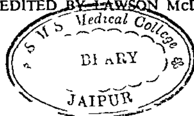
OF

OCCLUSIVE ARTERIAL DISEASE

PATHOGENESIS AND TREATMENT OF OCCLUSIVE ARTERIAL DISEASE

The Proceedings of a Conference held in London at the Royal College of Physicians of London 13th-14th November 1959

EDITED BY LAWSON McDONALD





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President's Opening Remarks

Fellows Members and guests of the College it is a great pleasure to me to welcome you again to the Royal College of Physicians for this the third of our post-graduate conferences It is also a great personal pleasure that they have become so popular but it is I am afraid a disappointment to a good many who had to be turned away after the ballot They are not here so I cannot apologize to them We will see whether we can improve this and whether there is some way of letting people know more quickly whether they can get a place or not But I think our original decision is correct to keep these conferences down to about 100 people which together with speakers and Chairmen means 120 or so to dine which is the most we can manage in our present premises though of course we shall have larger premises soon about which I shall speak at dinner time I think our decision to limit the numbers in this way was right We do not want the conferences to grow so large that people have no opportunity to get to know a few new colleagues and in very large gatherings it is more difficult to make people get up and talk and join in the discussions which I think are such an essential part of a conference of this kind I hope today you will not hesitate to get up during the periods of discussion You will notice from the programme that the arrangement is that there are one two or three speakers and then an interval for discussion Returning to the question of our being over subscribed it is rather interesting that I have had amongst other letters a letter from a senior Fellow of the College in London regretting that he was not able to come and asking couldn't a little priority be given to such as him ' and a letter from a rather junior member in the periphery saying couldn't a little priority be given to such as him as they have not so many opportunities and to both I gave the same reply namely that we want these conferences to be for all Fellows and Members to meet together and not for one particular section to be singled out As you know we aim at a high level but not so high in a technical sense that the practising physician would lose his interest

There are some demonstrations and one which is very important is a radiological one which Dr Bull has put up in the Committee Room Dr McDonald has a demonstration in the Library where you will be going for coffee and luncheon later on We are hoping also for a demonstration from Dr Poole in the Library I am not sure if it has been set up yet Now with regard to the speakers there are as you see a mixture of some of the distinguished names whom you have known for years and a number of younger men whose names you may not know so well the only selection being that they are people who are and have been actively engaged in research and study of the subjects about which they are going to talk

As you will see from your programme the conference divides itself conveniently into four sections first of all the section on Pathogenesis and then the three divisions the Cerebral Circulation the Coronary Circulation and the Peripheral Circulation

Now I think my opening five minutes is up and we start the conference with Dr Dible Would you please open the conference for us Dr Dible with your communication on Atheroma

PATHOGENESIS OF OCCLUSIVE ARTERIAL DISEASE

Chairman—Sir Robert Platt, Bt

Atheroma

J H DIBLE

It is unnecessary to describe to an audience of this sort the anatomical structure of the atheromatous lesion What I shall rather attempt to do is to trace its morphogenesis and from this to see what we can learn of its pathogenesis - both imperfectly understood subjects It is however necessary to ask that we should be more explicit than perhaps we generally are in the use of the term artery " All arteries do not have the same structure and doubtless this variation between let us say the aorta and a digital artery indicates a difference in function in nutrition and possibly in mode of reaction to injury This in the subject we are considering is well illustrated by the fact that below a certain size arteries are not subject to atheroma In an analysis of the distribution of obstructive lesions in ischaemic legs most of them subjected to amputation I found the following result -

Table I

Incidence of athero-thrombotic occlusive lesions in the arteries of chronically ischaemic legs

	Ant tib	Post tib	Peronl	Dors pedis	Lat plantr	Med plantr	Digitl
Wholly or partially obstructed	87	84	57	24	27	15	0
Patent	14	16	43	76	73	85	100

(The figures are percentages)

which shows the decline of the disease with the diminution in arterial size

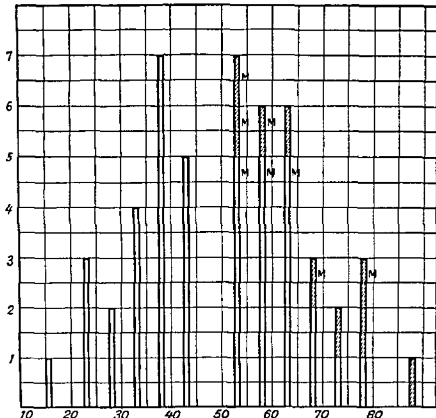
Moreover an artery" is a complex organ with at least four main structures which are involved in disease and may be involved independently or to different degrees These are the intima the internal elastic lamina the middle coat and the vasa vasorum

Coming now to the details of the histogenesis of atheroma I propose to devote myself in this brief sketch more especially to the musculo elastic arteries of the limbs which have

suffered some neglect in favour of the aorta and coronary arteries which is perhaps a pity The pathological lesion in the aorta has been described ad nauseam albeit without much light being thrown on its genesis and Professor Crawford is to deal with the coronary arteries Views on the pathogenesis of atheroma have passed through three main phases 1 The inflammatory-degenerative doctrine of Virchow which has more or less held the field for nigh on a hundred years 2 The slightly earlier thrombotic or incrustation theory of Rokitansky, which Virchow was thought to have discredited 3 The lipoid infiltration theory which gained its greatest fillip from the experiments of Anitschkow on feeding rabbits with large doses of cholesterol These different points of view are not mutually exclusive but represent foci around which discussions on the pathogenesis of the disease have centred Within the last ten years the thrombotic theory has been most ably resuscitated and extended in scope and detail by the work and writings of J B Duguid and I would say at once that for the purpose of this short communication I wholly accept Duguid s views which seem to offer the only satisfactory explanation of the very diverse and different pictures seen in atheroma But I would add that they need to be considered in conjunction with the peculiarities of the circulation in the arterial wall and mode of nutrition of its constituent parts The general hypothesis is simple enough the atheromatous patch represents a mural thrombus which has become covered with endothelium which partly "organises it from the surface whilst the deeper layers degenerate as a result of being excluded from the nourishment of the circulating blood

Atheroma is a degenerative disease and is intimately bound up with senescence in fact the philosophical argument of where the one begins to overtake the other is a matter which could be long debated In an attempt to follow the changes which occur in the vessels of the lower extremity and if possible to learn something of the genesis of atheroma Dr Duncan Taylor at my request removed samples of the anterior and posterior tibial arteries and of the dorsalis pedis at a stated level in an unselected series of bodies coming to post-mortem These were all examined by paraffin and frozen sections Altogether I have examined fifty bodies or limbs of this group the age distribution and incidence of classical atheromatous lesions being shown in the accompanying chart

There is the expected relationship between age and the incidence of atheroma and in addition it was found that all but one of the cases showing atheroma had eviden e of hypertension in the shape of heart-weight in excess of the accepted



Cha t l Age d t bution of f fty nd vidual w th the incid nc n th m of ath oma and Monck b rg l os s as determ n d by a s ngle t on from th arterie
Shaded a eas ndicate the cases of ath oma M ind at s Mon keberg le os s

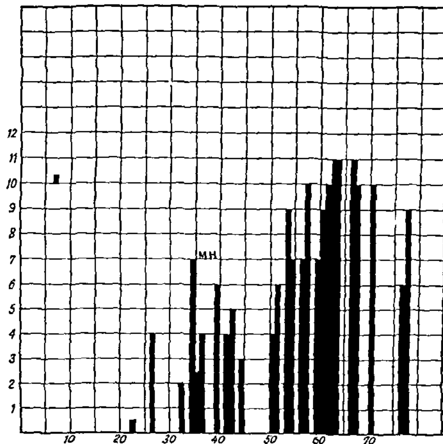
maximum The relationship with Ionckeberg s medial calcification is also shown six out of the nine atheromatous vessels showing the condition wh reas only three cases showed Monckeberg s disease alone I would stress that we are not dealing with the complete examination of the arteries I have named but only with a single sample of each at a stated level The result in so restricted an examination emphasizes how widespread must the disease be in the later age groups It also shows the close association between Ionckeberg s sclerosis and ath roma whilst Monckeberg s sclerosis can occur alone

I shall now turn to the cases in which atheroma was not found at the levels examined and ask were there any preatheromatous changes Here we come up against the problem of senescence and the recognition and interpretation of minimal

le~i r   As the individual grows older the arteries of the lower limb show changes in the internal elastic lamina which are well recognized but difficult to interpret   I show you pictures of these and you will see that there are changes in the intima which take various forms but in general lead to the production of numerous layers in place of the single layer of early life which itself generally persists and is recognisable   This is often called a "splitting of the internal elastic lamina" but I think the expression is inexact   The new elastic tissue is different in appearance and stains more weakly than the primary layer and the new secondary layers are not made up of a single homogeneous membrane like the primary layer but each consists of enormous numbers of new fine fibres mostly orientated in the long axis of the vessel and in transverse section appearing like the vertical posts of a stockade and so close together that when cut across they give the appearance of a single granular lamina on casual examination   The accompanying chart shows the incidence and thickness of this new internal layer in the series of cases we are now considering

These new elastic layers enclose between them cellular elements some of which are fibrous others muscular which lie in a ground substance" which histochemical examination indicates to contain a muco polysaccharide   What is the cause of this change and what is its purpose? We do not know   It does not appear to be constantly related to blood pressure as judged by heart weight   It is related to age   The only hint I can give of its abnormal production is that it is found in the larger renal arterioles in hypertension and in the single striking example of its precocious appearance in the present group it was associated with fatal hypertension

Is this a pre atheromatous condition and is it a necessary basis for the next stage? I propose to show you how the transition to atheroma may occur but there seems to be a missing factor in pathogenesis between the two conditions and I have frankly been disappointed in the paucity of transition stages which have appeared in this analysis   Possibly in a larger series this would not have been the case   We find from time to time evidence of two layers (at least) in the thickened intima suggesting successive phases of production which supports the incrustation theory   In these the normal senescent thickening which I have termed the secondary layer is overlaid with a less mature-looking tertiary elastic layer and sometimes at the surface of this we find fibro-cellular activity which may include foamy cells   the whole being covered with a thin layer of endothelium   These foamy cells stain for fat though the others may not do so   This is much



Cha t 2 The ncid nce and ext nt of intimal thick ning in the three arteries examined in each ind v dual Th o dinates ar arbit ary *figures for this the figure 12 indicating a thicknes equal to that* of the tunica media

what Duguid and others (Crawford Levine Rannie) have found on the surface of the aorta and coronary arteries An identical appearance is often to be found at the (growing) edge of a classical atheromatous patch where it abuts the secondary layer of intima which supports the view that the formation I have described is an atheromatous plaque in genesis

This is all comparatively plain sailing but we have yet a long way to go to reach the fully developed lesion and still further to explain it I think much of the explanation of this complex picture with its superficial fibrous layer its porridgy mass of fatty and caseous material its occasional deep blood vessels its anomalous deep fibrin and the haemorrhages both superficial and deep to which such attention has been paid is to be found in a consideration of the circulatory

conditions which develop pari passu with the further progress of the plaque The necrosis has always been explained as a result of ischaemia developing in the depths of the plaque - but this explanation is only acceptable if we assume that there are conditions present which prevent its vascularization In most situations in the body an ingrowth of vessels from all around would vascularize such an area but in the atheromatous plaque there are special conditions arising from the special blood supply An artery of the order we are considering has two sources of supply - the circulating blood and the vasa vasorum the two being independent and not communicating directly The barrier level dividing these territories I believe to be at the internal elastic lamina On the intimal side the presence of a mural platelet or dense fibrin thrombus provokes feeble and relatively ineffective attempts at vascularization - this has been admirably demonstrated by Crawford Levene Geiringer and others The medial vessels receive but little stimulus and their ingress is inhibited by or near the internal elastic lamina And so the vascularization fails It is instructive to contrast this with what occurs in a vessel which is acutely occluded by a rapidly forming red mixed or loose fibrin thrombus Here we see the most active growth of endothelial cells macrophages histiocytes etc and in short time the canalization and transformation of the thrombus into a sponge-work of circulatory channels which may go on to a partial restoration of the circulation In the most successful cases the new vessels develop an arterial structure (venous in veins) and sometimes a single new trunk may be formed within the old vessel (arteria in arteria) Such a picture may well be associated with an adjacent atheromatous focus which has precipitated the thrombosis but this is often not realised unless the vessel is cut in longitudinal section or the lesion followed in serial sections as was done by Duguid This canalization I believe to be essentially intra-arterial its function to restore a through-circulation and it does not primarily involve the vasa vasorum But the story does not end here If you examine a number of old atheromatous lesions you will find that in some of them there is an irruption of vasa vasorum towards the base of the plaque this however seems to take place at sites where the internal elastic lamina has disappeared I therefore suggest that the vascularization of the depths of the plaque which might prevent its necrosis and allow it to develop into a fibrous layer by the ordinary process of organization is prevented by the internal elastica barrier which has this function and exhibits it exquisitely in the process of canalization But once this barrier goes it becomes

possible for vessels from the external and middle coats to reach the depths of the plaque This they sometimes do and give us the picture of a fibrous instead of a necrotic base but this development is a late one uncertain and not very effective

The internal elastic lamina is also entitled to consideration in the genesis of atheroma on other grounds Often it is a site of early calcification the deposited calcium sometimes surrounding the lamina as if a special chemical affinity were present The fact that such calcium is later found deep in the plaque supports the view of the growth of the latter by progressive surface deposition Moreover the elastica itself is often a site of fat accumulation which suggests to some that the primary lesion may be at this structure and which may explain how we sometimes see two layers of fat in a well developed plaque

Finally we turn to the muscular middle coat In many atheromatous vessels the muscle is deficient indeed Thoma based a theory of causation on this finding Professor Crawford is also interested in this subject and you will have the benefit of hearing his views Not only may the muscle be deficient but the media may be unduly fibrous I have made an analysis of this change in the group of peripheral vessels I have concentrated upon in this paper and find that it is closely associated with the incidence of peripheral atheroma coronary atheroma excessive thickening of the intima a large heart hypertension and death from such cardio vascular conditions A common cause of fibrosis in parenchymatous organs is ischaemia and since myocardial ischaemia is a result of coronary arterial disease and the coronary arteries are only specially developed vasa vasorum analogy suggests that the vasa may play a role in the genesis of this puzzling condition

I am afraid I have done little beyond directing your attention to the various pieces of this jig-saw puzzle Whether they are all on the board and merely need more skilful orientating or whether the key piece is yet in the box the future will show

Other Occlusive Arterial Diseases

C V HARRISON

The list of "other occlusive arterial diseases" is a fairly lengthy one I have interpreted it as meaning those diseases in which the effects of arterial occlusion form a major clinical symptom or sign and I have further restricted it to the systemic circulation Even with this definition there are six separate diseases that can properly be included though I shall restrict my remarks mainly to two of them The six diseases in order of the size of artery involved are pulseless disease giant cell arteritis Buerger's disease polyarteritis nodosa scleroderma and thrombotic microangiopathy

Pulseless Disease

Let me confess that I have never seen an autopsy on a case of pulseless disease

The arteries involved are occluded by organized or organizing thrombus There is a variable degree of intimal fibrous proliferation The elastic tissue is fragmented and there is a heavy cellular infiltration of the media without fibrinoid necrosis The cells include histiocytes plasma cells and lymphocytes There are often granulomatous foci resembling tuberculosis with epithelioid cells and giant cells but acid fast bacilli are not found and guinea pig inoculations have proved negative There is a spread of inflammatory infilt-ation to the adventitia In some cases the aorta has shown medial damage resembling that of syphilis Veins are not affected Some authors have likened the appearances to those of Buerger s disease others have noted a likeness to giant cell arteritis though neither disease ordinarily affects young women or involves these arteries

Lessoff and Glynn have questioned whether the disease is really an entity So far the recorded data do not really justify any firm opinion as to the nature of the disease and I think we must reserve judgment Certainly we should be glad of the opportunity to examine material from any well established clinical cases

Pulseless disease

Age and Sex

Young women   Onset about age 20

Site of lesion

Innominate   subclavians and carotids

Site of ischaemia

Face (atrophy)   Eyes (peripapillary anastomoses)
Brain (vertigo)   Arms (pulseless)

Structural change

Thrombosis and intimal fibrosis leading to obliteration
Medial arteritis with elastic destruction often with giant cells   Aorta may be involved but not obliterated   Veins not involved

Giant Cell Arteritis is an undoubted entity both clinically and morphologically   Most of you will know the clinical aspects better than I do but some points in the pathology may not be so well known

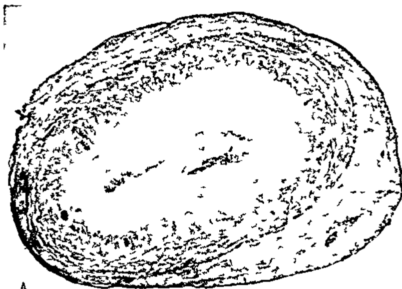


Figure 1   Giant cell arteritis   Temporal artery showing intimal thickening cellular infiltration and giant cells around the internal elastic lamina and fibrosis of adventitia (H & E x 40) (From Recent Advances in Pathology 6th Edition Churchill)



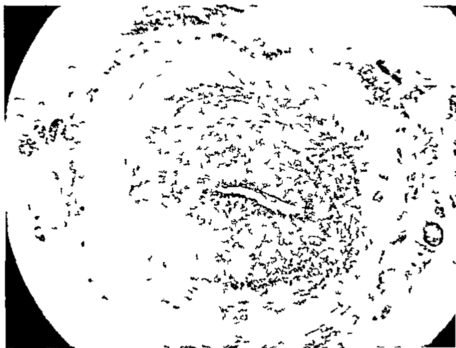
Figure 2 Giant cell arteritis Higher power of pa t of F g 1 to show giant cells around the fragmented elastic (H & E x 200) (From Recent Advances n Pathology 6th Edition Chu chill)

Firstly the extent of involvement of different arteries is much greater than was first thought Although the temporal arteries are most frequently and most prominently recognisable other cranial arteries are frequently involved In addition the following have been described as affected in published cases carotid cerebral subclavian suprascapular acromiothoracic axis radial, aorta, coronary iliac femoral and dorsalis pedis

Although occlusion of the lumen is the reason for including the disease in the present context aneurysmal dilatation can also occur Occlusion with consequent ischaemia occurs in the cerebral and ocular circulation and gives rise to the two serious complications of the disease A small minority of patients suffer cerebral softening but a far larger proportion suffer ocular ischaemia Fortunately this is transitory and incomplete in the majority but permanent blindness of one or even both eyes occurs in a significant minority of cases

On the other hand aneurysm formation occurs in some cases particularly in the larger arteries Before trying to discover why some arteries occlude and others dilate it will be convenient to describe the histological lesions The brunt of the damage appears to fall on the innermost layers of the media in the

region of the internal elastic lamina Here there is a brisk inflammatory reaction of mixed cell type including histiocytes, polymorphonuclears lymphocytes and plasma cells but rarely eosinophils At the same time the internal elastic lamina becomes fragmented and giant cells appear These are of foreign body type and lie in relation to the fragmented elastic Kimmelstiel et al (1952) have suggested that they arise in response to the damaged elastica The adjacent media may show fibrinoid necrosis The intima shows a brisk cellular hyperplasia of loose mucoid connective tissue so that the lumen rapidly becomes reduced to a slit or pin point Thrombosis of minor degree may overlie this but is not a significant factor in the reduction of the lumen Apart from these more striking changes there is a lesser diffuse inflammatory infiltration of the whole media and adventitia I should like to suggest that the fate of the arterial lumen depends on a race between the



Figu 3 G nt cell a te it B fo e t tm nt (H & E x 34)
(By kind permission of the Ed to B it h M d c l Journal)



Figure 4 Giant cell arteritis Same patient as Fig 3
(By kind permis ion of the Editor British Medical Journal)

medial damage and the intimal fibrosis If the former predominates the result is an aneurysm if the latter the result is occlusion To some extent the result depends on the size of the original artery If this is small it requires relatively little cellular proliferation to produce occlusion If on the other hand the lumen is wide great proliferation is needed to cause occlusion In addition to this, the distending force of the blood pressure is greater in a large artery The extreme example of this is seen in the aorta where the disease if it has any effect at all, produces an aneurysm This may be of two types either a saccular aneurysm or a partial rupture of the wall with a greater or lesser degree of dissection A number of deaths have been recorded from ruptured aneurysms There is

I think no doubt that giant cell arteritis is a real entity both clinically and morphologically but we have as yet no clue to its aetiology

Giant cell arteritis

Age and Sex

Either sex Middle age or elderly

Site of lesion

Temporal occipital carotid subclavian others occasionally

Site of ischaemia

Eyes Sometimes cerebral

Structural change

Occlusion by intimal fibrosis sometimes minor thrombosis Medial inflammation Elastic destruction Giant cells around fragmented elastic Veins very rarely involved

Buerger's Disease

Clinically this closely resembles ordinary atherosclerosis but it occurs at an earlier age and affects males almost exclusively The curious legend that it is specially common in Jews dies hard It is unfortunate for the pathologist that by the time gangrene makes amputation necessary the arterial lesions are usually in the state of scarring and in fact many of the illustrations in text books are of such old scarred lesions At this stage it is difficult to distinguish Buerger's disease from the late effects of simple thrombosis and some workers have even denied the existence of Buerger s disease as an entity In fact the early stages are quite different The earliest change appears to be a sudden thrombosis in situ with a red unlaminated clot Very soon a series of acute inflammatory foci form in the periphery of the thrombus These contain numerous polymorphonuclears and may contain giant cells There is a loose cellular infiltration of the wall and a brisk vascular response by the vasa vasorum which stream through the media from the adventitia into the thrombus One important point is that the media does not suffer necrosis and the elastic lamina remains unbroken The result is that in the scarred stage the elastic lamina remains as a deeply crenated band surrounded by a contracted but intact media One further difference is that in Buerger s disease there is a great deal more perivascular inflammation and subsequent scarring than in ordinary thrombosis

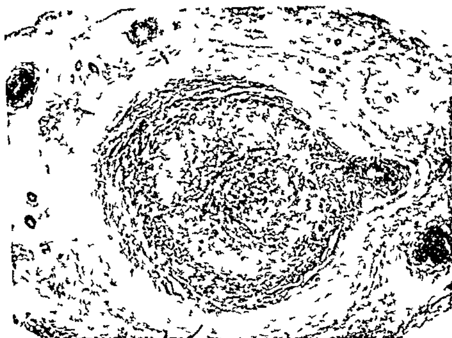
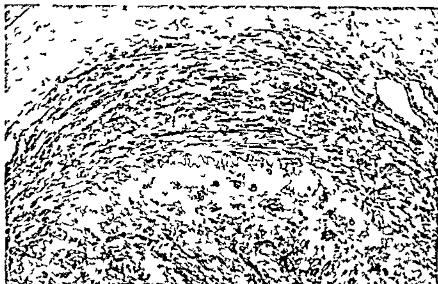


Figure 5 Buerge disea e The lumen is occupied by actively o ganising thrombu There a fibrous thickening of the adv nt t a (From Recent Adv nc in Pathology 6th Edition Churchill)

As you know the veins are regularly involved in Buerger s disease and the lesions in them are remarkably like those in the arteries Since they are often used for biopsy in order to establish the diagnosis much of our knowledge and experience is based on the study of the venous lesions - many of Buerger s original illustrations were of veins This is incidentally a sharp point of difference from giant cell arteritis in which veins are very rarely involved though I have seen one case with venous involvement and a few have been described in the literature



F gure 6 Buerge s d sease H gh power vı w of pa t of Fig 5 to show th ntact last c lamına the absence of m dial de t uction and the dıffu e cellular ınfılt ate
(F om R cent Advance ın P thology 6th Ed t on Churchıll)

Buerger's disease

Age and Sex

Males 30-50 years

Site of lesion

Popliteal to foot Odd reports in other sites

Site of ischaemia

Foot and leg

Structural change

Segmental or focal Thrombosis followed by inflammation with peripheral abscesses in thrombus Diffuse inflammation of media and adventitia and periarterial connective tissue without necrosis Veins involved

Polyarteritis Nodosa

Under this heading I should like to make one poirt that

the disease can take three rather different forms First there is what one may perhaps term the classical form This is the one that may give rise to ischaemia in various organs or tissues Secondly there is the form recognised by Rose and Spencer as polyarteritis with pulmonary involvement This is the form that commences with a chronic granulomatous lesion somewhere in the upper respiratory tract and later shows signs of arterial involvement and produces granulomatous and arterial lesions in the lungs and which also produces curious granulomatous lesions in various organs Finally there is the type described a few years ago by Dawson Ball and Platt and characterized by involvement of very small arteries or arterioles and accompanied by an explosive glomerulitis This form usually has singularly little involvement of medium-sized arteries and a consequent absence of ischaemic changes



Figure 7 Polya teritis nodosa Aorta showing patchy m dial and ove lying intimal th ck ning (The pale foci repre ent ar as of loss of l stic tissue) (Elastic and van Gieson x 36)

To return for a moment to the classical form of polyarteritis one of the places where it produces ischaemia is in the kidneys and Rose and Spencer offer evidence for the view that any hypertension that accompanies polyarteritis is a secondary

one due to renal ischaemia One recent point I have recently had a case of polyarteritis in which the media of the aorta was involved This may be of no significance but it is perhaps worth considering the possibility of polyarteritis and looking at other smaller arteries in those occasional cases of unexplained non-syphilitic aortitis that we encounter every now and then

Polyarteritis Nodosa

Age and Sex

Both sexes Any age

Site of lesion

Three variants

1) Classical
2) With pulmonary involvement
3) Microscopic

Affects visceral arteries

Site of ischaemia

Visceral and nerves

Structural change

Medial necrosis with scarring Elastic always destroyed
Intimal fibrosis and thrombosis Veins often involved
Heavy cellular infiltration

R E F E R E N C E S

Polyarteritis

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Giant Cell Arteritis

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Experimental Atheroma

Sir HOWARD FLOREY

I have been asked to speak on experimental atheroma and I suppose that what is required is something about how lesions resembling atheroma in man can be produced in animals Why do we go to the trouble of trying to produce lesions in animals when they are unfortunately so admirably and frequently displayed in man? At the present time we can do a number of experiments on man for example by employing the methods elaborated by chemists and biochemists it is possible to follow the level of *cholesterol and other lipids in the blood to determine the* effect of sex hormones on this level to observe the effects of *unsaturated fatty acids and so on Why then do we need an* animal with atheromatous lesions I think the short answer is that we cannot vary the diet and other environmental factors of man in a completely uninhibited fashion and there is from the experimental point of view the regrettable feature that it is not possible to kill our subject at any given moment So we fall back on animals and as is true for most chronic diseases it has proved difficult to reproduce in an animal a lesion which everyone accepts as being exactly similar to that which occurs naturally in man The literature on the work done on animals is vast and there are many extensive and competent reviews on this subject (Anitschkow 1933 Hueper 1944 1945 Duff and McMillan 1951) This morning I shall only be able to pick out a few points from this vast array of data - points which I personally think are important and possibly of interest to you

The experiments which are most widely known and which so far have had most influence on ways of considering the pathogenesis of atheroma in man are those dating from the work of Ignatovsky in 1908 He found that rabbits fed what he thought was a protein-rich diet developed lesions in the aorta It was shown by Anitschkow and Chalatoff in 1912 and 1913 that atheromatous lesions could be produced in rabbits by feeding large quantities of cholesterol independently of protein

The rabbit a herbivorous animal normally has a low level of cholesterol in the blood but if it is fed cholesterol

dissolved in oil or mixed with its food in other ways it quickly develops very high cholesterol levels in the blood and macroscopically visible atheromatous lesions in the aortic intima follow in a matter of a month or so

The lesions that appear particularly in the thoracic aorta are characterized by the early accumulation of lipids in the subendothelial tissue

How does the fatty material reach the intima? Does it pass through or between the endothelial cells or is it carried in by mobile cells? Perhaps it might interest you to see two electron micrographs of the intima of the rabbit which enable one to visualize it more clearly than is possible with more usual methods (see Figures 1 and 2)

During cholesterol feeding more and more cells collect in the space between the endothelium and the internal elastic lamina Anitschkow thought that the endothelium was not involved



Figu 1 The intima of the aorta of a normal rabbit E endothelial cell on the urfac in some of which nuclei can be se n CJ cell junctions IL internal lastic lamina which can be se n to be f n strat d e g at F ET sections of elastic tissue fibres between IL and E The fine dots a collag n fibril SM smooth mus l cell below IL Mag X 2 600



F gur 2 Normal rabb t aorta Th l tte ing m ans the same as for F g 1 In this specimen a cell (A) can be e n inte pos d between the endoth lium and th int rnal elastic lamina Mag X 10 500

in this process but recently Poole Sanders and I (1959) have been able to show that in fact the endothelium takes up sudanophil material

This observation has been amplified by Parker (1960) who has demonstrated that in the cholesterolaemic rabbit "caps" probably composed of protein and lipid are seen to be applied to some of the endothelial cells of the coronary arteries Small projections from these caps appear to be entering little caveolae on the surface of the cell which are then supposed to be nipped off thus enclosing the lipid within the cytoplasm He has also demonstrated some large vesicles probably caused by lipid accumulation in the endothelial cells

There is then good evidence that in this form of experimental atheroma the endothelial cells are involved in the process I mention this because as far as human lesions are

concerned, I believe that very little attention has as yet been paid to the possibility that initial lesions may occur in the endothelium Possibly macrophages are involved in the transport of lipid into the intima Leary in particular believes that the collection of macrophages in experimental atheroma is a collection of cells which have arrived there from the blood stream This may be possible, as we have seen macrophages on the surfaces of rabbit plaques and between endothelial cells but it is not known in which direction they are moving (Poole et al 1959)

Other changes were observed by Dr Parker in cholesterol fed rabbits He observed very early changes in parts of the internal elastic lamina which appeared to swell up and to alter its appearance This change could occur within 24 to 48 hours of the institution of acute lipaemia

With the passage of time the lesions in the rabbit provided the diet is continued increase in size the amount of fibrous tissue increases the internal elastic lamina breaks up and some of the fat is liberated from macrophages to form a pool of free fat at the base of the lesion There may be calcification in this, but at no time is there any ulceration such as occurs in the human lesion nor has thrombosis been observed either in the aorta or in the coronary vessels Lesions are not found in cerebral vessels

There is another substantial difference also from the human disease and that is that in the rabbit not only is the cholesterol deposited in the walls of the aorta and coronary vessels but it also accumulates in large amounts in certain organs particularly the liver and spleen

The main point then is that from the observations on rabbits subjected to dietary manipulation lesions can be produced in the aorta and coronary vessels which bear a considerable resemblance to the lesions of man though they are not identical

It has also been found that lesions can be produced in chickens by feeding cholesterol and a great deal of work has been done on chicken atheroma Again the lesions are associated with a high blood cholesterol consequent on the feeding of large amounts of cholesterol in the diet Such chickens have been subjected to many experimental procedures which I shall not have time to mention here There is a monograph on the subject (Katz and Stamler 1953)

Until relatively recently it had not proved possible to produce similar atheromatous changes by feeding diets rich in cholesterol to such an animal as the dog but Steiner Kendall

and Bevans (1949) discovered that changes could be produced in the intima of dogs if they were fed a diet high in cholesterol after having had their thyroid function depressed by the administration of thiouracil You will recall that atheroma is apt to be much more marked than usual in myxoedematous persons

Intimal lesions have also been produced in Cebus monkeys by feeding a cholesterol-rich diet in which there was a lack of the amino acid methionine (Mann Andrus McNally and Stare 1953) All these changes have as their root the feeding of excessive amounts of cholesterol

Quite recently it has been shown that it is possible to produce atheromatous lesions in rabbits without feeding an excess of cholesterol and indeed on a fat-free diet Malmros and Wigand (1959) gave rabbits a semi-synthetic diet which contained little or no fat They noted that there was a very steep rise in the blood cholesterol which is normally well below 50 mg per cent What might be of interest to human pathology is that on this diet which produces a high level of blood cholesterol a dramatic change was caused by adding to the diet oils rich in poly-unsaturated fatty acids the acids which some people like to call essential fatty acids It may be that this experimental work on rabbits will be of very considerable significance in assessing the possible role of a lack of poly-unsaturated acids in the diet in the genesis of human lesions

Rinehart and Greenberg (1951) have shown that pyridoxine deficiency in monkeys will result in atheroma-like changes in the aorta The changes are characterised particularly by the accumulation of mucosubstances which stain metachromatically with toluidine blue

Although these lesions can be produced in monkeys by the deprivation of pyridoxine there is no evidence that they have any relationship to the lesion which occurs in man for it is improbable that man frequently suffers from a sufficient degree of pyridoxine deficiency

I should like to mention another line of work Recently a very interesting paper was published by Clarkson Prichard Netsky and Lofland (1959) on a naturally occurring atheroma in pigeons The lesions which they describe and which they figure are almost if not quite indistinguishable from those occurring in man They are apparently real atheromatous lesions with accumulation of cholesterol and macrophages fibrous tissue and all the rest The particularly interesting thing about this natural atheroma is that it is not produced by dietary manipulation The pigeons were fed solely on various grains It has been found that only certain strains of pigeon are subject to

this form of atheroma whereas pigeons fed on the same diets but of different strains seemed to be quite immune The investigations, which are now no doubt being actively pursued in the United States have clearly shown that there is no sex differentiation in the liability of the pigeons to contract atheroma It is apparently entirely genetically controlled and it does not appear to be associated with dietary factors The future will show whether this lesion in pigeons can throw light on the development of the human lesion

There are other possibilities in the investigation of what might be called naturally occurring atheroma Lesions have been described in a very large number of wild and domestic animals Recently we had an opportunity to examine in some detail part of the vascular system of a pig which had been in the department for over seven years during the last four of which it had been consuming a diet which was rather poor in fatty material Nevertheless it had well marked atheromatous plaques in the aorta and what perhaps is rather more interesting there were lesions in the coronary and cerebral vessels These plaques were strikingly similar to some lesions occurring in man

These observations perhaps make more significant those reported by Rowsell Downie and Mustard (1958), who kept young pigs on various diets They found that atheromatous lesions were more prominent in the pigs fed butter than in those fed margarine or no fatty supplement

Baboons also appear to develop atheroma and they are being investigated but this animal is not very convenient to handle

It is clear from what I have said that I do not consider that any of the experiments so far performed have given a clear cut answer to the many problems posed by human atheroma but what is I think quite apparent is that it may now be possible to elaborate observations made on man in a more comprehensive manner on animals than is possible on man Experimental pathology must be very closely linked with experimental medicine, and I think that the way is now fairly clear for such to be possible

I am indebted to Mr D W Jerrome for making the sections for the electron micrographs and to Mr F Bradley for assistance with photography

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Metabolism of Lipids in Relation to Atheroma

G J POPJAK

The hypothesis that a correlation exists between the pathogenesis of atheroma and metabolism of lipids is worthy of attention, (a) because the earliest lesion the pathologist sees in atheroma is the accumulation of lipid material in intimal cells and intimal thickenings (b) because of the greater prevalence of atheroma in patients with disturbed lipid metabolism, particularly with a permanently elevated blood cholesterol level (c) because patients suffering from atherosclerosis taken as a group have plasma lipid levels (especially plasma cholesterol levels) higher than those not similarly afflicted and (d) because the only means by which a lesion simulating human atheroma may be produced in experimental animals is the induction of hypercholesterolaemia by dietary means Far be it from me to say that a disturbance in lipid metabolism is the sole cause of atheroma nevertheless an association between atheroma and lipids cannot be denied and appears to be the most common thread linking the varied forms of this disease together

More specifically among the various substances classed as lipids cholesterol and its esters are the most highly favoured suspects as being the villain of the piece This suspicion has been harboured perhaps ever since Vogel established in 1843 the invariable presence of cholesterol in atheromatous lesions, and was much strengthened by the production of experimental atheroma in rabbits by Anitschkow and Kalatow at the beginning of the century by the administration of a diet rich in cholesterol

In atheromatous lesions 25 to 30 per cent of the dry matter may consist of lipids 75 to 80 per cent of which is sterol (mostly cholesterol) About two-thirds of the cholesterol in atheroma is esterified with fatty acids and about one-third is in the free form Elspeth Smith (1959) reported recently that there is also a characteristic change in the phospholipid composition of atheromatous lesions of the human aorta Whereas in the lipids of normal aortic intima 45 to 50 per cent of the total phospholipid is accountable as sphingomyelin in

atheromatous lesions as much as 80 per cent of the phospholipids is apparently sphingomyelin

I feel extremely reluctant to quote any figures beyond these generalities as to the lipid composition of human atheromatous lesions I have searched in vain for an account in which the morphological appearances of the various atheromatous lesions might have been correlated with data of biochemical analysis With the present-day methods of microanalysis such investigation should be quite feasible and offers a good scope for fruitful collaboration between the pathologist and the biochemist

In spite of the enormous amount of research all we can say at the moment is that there is an association between the development of atheroma and the metabolism of cholesterol but as to the closer links no one can offer a hypothesis that might be universally acceptable There are two main rival ideas one contends that blood cholesterol associated with β-lipoprotein is the causative factor and the other seeks an explanation in the metabolic activity of the arterial wall itself I would like to discuss our present-day knowledge of cholesterol metabolism in relation to these two ideas and to point out what measures might be at our disposal to influence the development of atheroma provided either of these two principal ideas bear any relation to the truth

Cholesterol is an interesting substance because it is exclusively an animal product although there are substances related to it in plants yeast and fungi none of the main plant sterols such as ergosterol sitosterol etc which carry a substituent chemical group on carbon atom 24 is convertible by animals into cholesterol

As far as man is concerned cholesterol in the body is derived from two sources one is endogenous synthesis and the other is the diet Although many tissues in the body are able to synthesize cholesterol from the point of view of the origin of plasma cholesterol we need to concern ourselves only with the liver

From data obtained by the use of isotopic tracers there is a fairly unanimous agreement among the various investigators that approximately 1-1 5 g of cholesterol is manufactured daily in an adult s liver the total cholesterol content of the organ being 3-5 g Quantitatively the most important pathway for the elimination of cholesterol is its transformation into bile acids the daily production of the latter being about 0 8 g Much of the bile acids secreted into the intestine is reabsorbed only a small portion equivalent to the daily formation from choles-

terol being lost in the stools There is also an intestinal elimination of cholesterol, the amounts of faecal sterols being about 0 3-0 5 g /day Plasma cholesterol represents rather a large pool and its turnover time is estimated to be 14-20 days which means that approximately 0 5 g of cholesterol moves out of the liver into the plasma each day All these figures add up to a fairly good balance sheet the daily production being about equal to the daily elimination This is so provided we ignore the contribution from the diet which of course is variable On a diet which contains 2 eggs 5 ounces of meat 1 pint of milk and 1 ounce of butter our daily intake of cholesterol may be as much as 1 g equivalent to more than one-half of the amount produced by the liver Clearly, an accumulation of cholesterol in the body may result from a supply greater than the elimination

I would like to examine now in general terms the possible means at our disposal to decrease the accumulation of cholesterol in the body

(i) Inhibition of absorption Generally there is an objection against the suggestion that dietary cholesterol might be responsible for an increased plasma cholesterol level on grounds that deliberate attempts to raise the concentration of plasma cholesterol in man by cholesterol feeding have largely failed One might quote in this context the experiment of Cook (Cook et al 1956) who consumed 6 9 g of cholesterol in the form of a dish of 20 scrambled eggs and failed to observe an increase in his plasma cholesterol in spite of the fact that 5 g of the "dose" was absorbed One has to assume that these 5 g were deposited in the tissues Perhaps the levels of cholesterol in the plasma that we have come to regard as normal are in fact constantly elevated owing to our regular consumption of cholesterol in the diet That this is not too wild a suggestion is borne out by the fact that a cholesterol-free diet or administration of substances which interfere with the absorption of cholesterol usually lower blood cholesterol levels β-sitosterol a plant sterol found most abundantly in soya bean has a structure very similar to that of cholesterol except that it carries on the side-chain in position 24 an ethyl substituent This sterol is hardly absorbed at all from the intestine nevertheless it inhibits very much the absorption of cholesterol It prevents in experimental animals the production of hyperlipaemia and atheroma by cholesterol feeding and also lowers plasma cholesterol levels in man To achieve this rather large doses of sitosterol 8-20 g /day have to be taken The cholesterol lowering action of sitosterol may be attributed to the inhibi-

tion of the absorption not only of dietary cholesterol but also of the absorption of cholesterol secreted into the lumen of the intestine with the bile

(ii) Increased elimination of cholesterol and its breakdown products In spite of the possibility that the regular consumption of cholesterol in the diet may be one of the factors in the initiation of high plasma cholesterol levels and hence (?) of atheroma the more generally held view is now that not so much dietary cholesterol but the nature of the fat in human diets is the responsible agent No doubt Dr Morris will deal with this aspect of the problem in detail I might merely summarize here briefly the results of world wide surveys which showed very clearly that there was a very strong correlation between the nature of dietary fat and (a) the incidence of severe atheroma with clinical complications and (b) plasma cholesterol levels In countries or in social groups within a country where the consumption of the fat of land animals is high there is a high incidence of severe atheroma and of its clinical manifestations and also of high blood cholesterol levels Conversely the consumption of liquid vegetable seed fats favours the lower incidence of atheroma and of lower plasma cholesterol levels (for review cf Brontë-Stewart 1958) Furthermore it has been shown by carefully conducted experiments on patients in as widely different centres as New York Cape Town Ontario California and Sweden that fats which contain a high percentage of saturated fatty acids raise plasma cholesterol and fats which are rich in fatty acids containing more than one double bond lower the plasma cholesterol Now animal fats usually contain less than 10 per cent whereas a number of the vegetable seed fats may contain as much as 50-75 per cent of these poly-unsaturated fatty acids

It has been a well recognized fact for many years now that a large proportion of the fatty acids associated with esterified cholesterol is usually of this highly unsaturated type Although young growing animals deprived in their diet of the poly-unsaturated fatty acids develop a definite deficiency syndrome which can be cured by linoleic and arachidonic acids it is a matter of controversy whether any disease in man is attributable to deficiency of these so-called essential fatty acids James and Lovelock (1958) could not demonstrate a significant difference between the essential fatty acid content of plasma lipids of normal patients and of those with clinical manifestations of occlusive arterial disease On the other hand Dr Sinclair informs me that a German group of workers (Schrade et al) reported recently at a meeting in Baden-Baden that they find a

consistently lower content of essential fatty acids in the plasma lipids of patients with coronary atheroma than in the plasma of matched controls Whatever might be the case it is an undeniable fact that fats rich in polyunsaturated fatty acids decrease plasma cholesterol levels

Although the evidence on the question of the mode of action of these highly unsaturated fats is far from complete data reported from several laboratories show that the rate of elimination of cholesterol and of its breakdown products is substantially increased during ingestion of polyunsaturated fats Lewis working at St George's Hospital London (personal communication) found for example that cholesteryl esters of the β-lipoproteins which were prepared from the blood of animals fed a highly unsaturated vegetable fat in their diet after intravenous injection to normal animals were eliminated much faster than the cholesteryl esters obtained from animals kept on a butter-fat diet The evidence suggests that cholesterol esterified with polyunsaturated fatty acids is metabolized faster than cholesterol esterified with saturated fatty acids

(iii) Inhibition of endogenous synthesis of cholesterol The biosynthesis of cholesterol is perhaps the most complex of all biosynthetic processes yet unravelled Through the work of Bloch in the U S A of Lynen in Germany and of our own we have come to realize that over twenty distinct enzymic reactions are involved in the formation of cholesterol (shown in an abbreviated form in Figure 1)

Theoretically one could stop the formation of cholesterol by interfering with any of these reactions One physiological control appears to be between acetyl-coenzyme A and mevalonic acid very likely between hydroxymethylglutaryl-coenzyme A and mevalonic acid and the most probable point of action of some hormones (e g of thyroxine) is the reduction of hydroxy-methylglutaryl-CoA to mevalonic acid A few years ago phenyl substituted fatty acids phenylacetic and α-diphenylylbutyric acid, were introduced by Italian workers for the inhibition of cholesterol synthesis These substances have been claimed to reduce plasma cholesterol levels in patients on prolonged administration The mechanism of action of these compounds seems to be an interference with the formation of acetyl-CoA because of this property I feel that they are rather undesirable antimetabolites and are likely to be toxic Acetyl-CoA is a vital intermediate not only in the synthesis of cholesterol but also in several very important metabolic processes and therefore interference with its formation is most undesirable

There appears to be a new possibility now of a specific

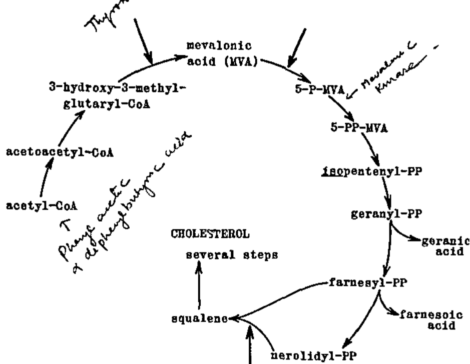


Figure 1 Reaction s quence of cholesterol biosynthesis in an abbreviated form The th h avy arrows ind cate points of physiological control in th sequence

inhibition of the endogenous synthesis of cholesterol During the last year we have found in my laboratory that some of the intermediates in the biosynthesis of cholesterol namely geranyl-pyrophosphate and farnesyl-pyrophosphate are also metabolized on an alternative pathway to the acids geranic and farnesoic acid (trans-trans 3 7 11-trimethyldodeca-2 6 10-trienoic acid) These acids are not intermediates in the biosynthesis of cholesterol On the contrary (a) they represent a route for the elimination of too high concentration of intermediat s and (b) if present in sufficiently high concentration they inhibit cholesterol synthesis This inhibition is brought about by an interference with mevalonic kinase the enzyme responsible for the formation of 5-phosphomevalonate (5-P-MVA cf Figure 1) and also by preventing the utilization of farnesyl- and nerolidyl pyrophosphate for the synthesis of squalene the latter being a near precursor of cholesterol

It seemed therefore a logical step to test analogues of these acids as possible inhibitors of cholesterol synthesis

My colleagues Dr and Mrs J W Cornforth at the National Institute for Medical Research synthesized for me farnesoic acid and its saturated analogue 3 7 11-trimethyldodecanoic acid The Merck Sharp and Dohme Research Laboratories Rahway New Jersey, U S A provided me with some further analogues among which one the 3-hydroxy-3 7 11-trimethyldodecanoic acid, seems particularly likely to be of some use

The three acids mentioned farnesoic acid and its two analogues have been tested among other substances as inhibitors of cholesterol synthesis Until now only small amounts of material were available for the tests, which were all done in vitro with liver homogenates The results of Table 1 show

TABLE I

Inhibition of Cholesterol Synthesis from 2-^{14}C-mevalonate in vitro by Analogues of farnesoic acid

Substance (as K-salt)	Concentration mM	% Inhibition
Dodecanoate	1 0	No inhibition
Farnesoate	0 4	27 5
	1 0	31 0
3 7 11-trimethyl dodecanoate	0 2	35 0
	0 4	54 0
	1 0	100 0
3-hydroxy-3 7 11-trimethyl-dodecanoate	0 2	24 0
	0 4	93 0
	1 0	100 0

that all three substances inhibited cholesterol synthesis With farnesoic acid the inhibition was moderate the two analogues on the other hand caused inhibitions at such low concentrations that we are encouraged to test them in vivo Unfortunately we have obtained only a few days ago sufficient supplies of these substances for experiments in whole animals therefore I am unable to report further on their possible usefulness

Interference with the absorption of cholesterol from the intestine an enhancement of sterol elimination and an inhibition of endogenous synthesis of cholesterol are the three ways in which at present we might decrease the cholesterol content of the body and diminish the chances of development of atheroma if the hypothesis that too much cholesterol in the body is harmful is correct

I mentioned at the beginning that another idea, championed particularly by some American workers (e g Werthessen 1959 Zilversmit 1959) seeks an explanation in the metabolic

activity of the arterial wall itself for the development of atheroma It has been shown in several laboratories that arterial walls e g the wall of the aorta are quite active in synthesizing lipids particularly cholesterol and phospholipids Whether this metabolic activity is sufficient for the development of atheromatous deposits is not clear at present However if the synthetic activity of arterial walls should prove to attain pathological levels the use of specific inhibitors of cholesterol biosynthesis might be also of value

This presentation of the possible correlation between lipid metabolism and atheroma has been of necessity sketchy and coloured by personal views and interests If I may I should like to raise one last question If an interference with the metabolism of cholesterol along the lines I discussed should prove ultimately of value in inhibiting development of atheroma at what period of an individual s life should such interference begin? The feeding of highly unsaturated fat to patients with coronary occlusion has become rather fashionable but while the treatment is not harmful I do not think that there is as yet any evidence to show that such treatment helps the patient during recovery from an acute occlusion or that it influences the subsequent course of events I hold with those pathologists who maintain that atherosclerosis develops in stages the earliest of these being the pure atheroma with it lipid deposits these earliest stages of the disease are more likely to be reversible than the later ones I feel therefore that some form of treatment aiming at reduction of plasma lipid levels should commence years before degenerative arterial disease manifests itself clinically An impractical suggestion of this sort could come only from a biochemist

R E F E R E N C E S

The subjects discussed in this brief communication have necessarily been condensed from a very large volume of published work and therefore it has not been possible to discuss individual articles with the exception of a very few which have been mentioned to illustrate specific points

General information concerning the metabolism of cholesterol (biosynthesis absorption elimination etc) and the action of various substances on cholesterol metabolism may be found in various chapters of two recently published books both bearing the title Cholesterol" one edited by R P Cook and published by Academic Press New York (1958) the other written by David Kritchevsky and published by John Wiley & Sons New York (1958) "Hormones and Atherosclerosis" edited by Gregory

Pincus and published by Academic Press, New York (1959) contains much detailed discussion about the relation of metabolism of lipids to atherosclerosis "Essential Fatty Acids" edited by H M Sinclair and published by Butterworths Scientific Publications London (1958) presents in individual articles much of the present trends of research on the metabolic significance of polyunsaturated fatty acids

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DISCUSSION

DR RAE GILCHRIST: I find the pathology of arterial disease unusually complex and difficult to understand It eems to me that so much is conjectur d and so much is still sp culative that I would like to ask the pathologist is it fair to conclude that what we are seeing in these beautiful slide which they have hown u represents two proces es a diffuse deg nerative proce s through the arterial tree and secondly a local thrombotic process? Professor Dible showed a b autiful slide and emphasiz d the importance of int rnal thickening I would like to ask him - does he suppo e that the tertiary layer to which he referred is th result of repeated d position of minor hr ds of fibrin? It eems to me that you can go on with thi deg n rative process safely for years and years and then s mething det rmin s the localized d position of the occlu ive lesions I would like to a k him if he can offer us any explanation of the localization of the plaque and is it in his opinion primarily fibrin? The cond qu tion I would like to put is are th s odd forms of arteritis Buerger s disea e giant cell arteritis etc reproduceable in the exp rimental animal and with what results?

PRESIDENT: That seems to call for an answer first by Prof or Dible and secondly by Profe sor Harrison

PROFESSOR DIBLE: I was asked wheth r there are two processes a diffuse degeneration and a local thrombotic one I think the evidence i ye I think the diffus degeneration if you can call it this is a change as o iated with s nescence Diffuse degen ration is a thing we all have and it se ms to be inevitable The local atheromatou le ion is something which is superimposed without any degr e of inevitability and ometimes it is of course impo ed upon an arterial wall which for all practical purposes we must call normal The oth r thing I think I was asked refers to the tertiary layer: is it a result of repeated d position and is it made up of fibrin? I think it is a r sult of rep ated continuous ac retion and I think a good deal of it is fibrin but I think that the fibrin is d posited pari pa su with an accumulation of cells Which comes first I am not prepared to say I do not think we have suffi ient information

PROFESSOR HARRISON: Giant cell art ritis: I know of no publication in which anyone has succ eded in reproducing anything that really look like it Poly-arteritis nodo a: in Rich and Gregory s work and in all ubsequent on s they get pretty n ar the fine type of arterial diseas but I do not think anyone ha managed to produc convincing lesions in larger arteries Bu rger s disea e: th re have been a number of attempt and the be t I know is that of Dr Sheikh in Cameron s laboratory at *Univ r ity College Ho pital* but *really not v ry close* I think the answer in two words is not yet

PROFESSOR M MICHAEL: I have enjoy d this morning s papers

enormously I should like to ask have any of our distinguished pathologists got any views on the curious localisation of atheroma in certain elective sites -pulmonary arteries lower part of the aorta abdominal aorta particularly occlusive changes which are singularly prone to develop in the femoral artery (Hunter s canal) and of course the vessels supplying the brain? In other parts the deposition of whatever it may be seems to be so slight and so late

DR OSBORN: I think the changes of atheroma are so complex in the adult that to understand them we have to go back to the child If I might show you some slides of the beginning of the atheromatous process in children it might help First of all in the foetus and newborn we get a lot of mucoid lesions of the great arteries of the aorta and its main branches Just what they mean I have no idea The artery in this slide is a coronary artery from a boy aged only seventeen who was killed in a motor car accident and you will see that his main left descending coronary artery is almost completely occluded When we go back to smaller children still the first lesions are found to be an infiltration of mucinous substances and vitelloids I am not at all sure which comes first The supply of material is not great and in my cases so far the mucins and the lipids have appeared together and my impression is that these come before there is any cell exudate at all This slide shows a higher view of this artery of a boy of seventeen and this actually has the accumulation of lipids and there are mucins which we will show you in a minute and there is the last lesion of the lot in the lumen a little accumulation of fibrin on the endothelium This slide is stained with toluidine blue and is somewhat similar to the one that Sir Howard Florey showed us with purple staining mucin shown near the lumen and again running round the side but not pr sent in the lipid part in the centre

If you do a trichrome stain you can generally appreciate the extent of the vascularity of these lesions which you do not appreciate otherwise Now I do not know if you can distinguish through that artery a lot of small capillaries but I feel satisfied through looking at these in children that the haemorrhages and so on are a late stage and that the fibrin part is not primary at all

PRESIDENT: Would anybody like to answer Professor McMichael s question on localisation?

PROFESSOR DIBLE: I do not think anyone knows the answer I would say that the increased thickened layers of intima which I demonstrated as a secondary phenomenon seem to be greatest round the orifices of the intercostal arteries where it is known that atheroma occurs The other fact which always appeals to pathologists is the relationship between syphilitic disease of the aorta and atheroma Everyone knows that the arch of the aorta is not one of the sites of major atheromatous exchange but in syphilis where we have gross alterations in the media and also in the vasa vasorum we get gross atheroma in that site Those are two pointers but I do not know what the complete answer is May I say something about the other questions now?

I think the importance of the examination of changes in children is very great and I also agree with the sp aker that mucinous change is often pre ent and I think that it may precede cellular accumulations and that cellular accumulations are not invariably associated with lipids I think that one has to be very sceptical about the interpretation of the capillaries in these atheromatous plaqu s It is so easy to get cleft that are not capillaries and to be led to believe that they are capillaries

DR COWEN: Relating to Professor McMichael point I understand that with regard to the carotid circulation the lesion is nearly always on the internal carotid ju t above the junction with the external carotid Do Professor Dible and Professor Harri on find thi area always? It is not at the junction but a little higher and seems to be on the vessel of higher pr ssur rather than one of lower pressure

The second question I would like to a k is for Dr Popjak I there any real explanation of the two sorts of fat absorption in man the very interesting thoracic duct one - is that a que - tion of particle size only as opposed to the venous portal blood absorption of the other? It seems a vital point that never seems to be very well explained

DR POPJAK: I think that the primary pathway of absorption is via the thoracic duct and the ab orption via the portal vein is really negligible and can be demonstrated only for such hort chain substances as tributyrin whi h are water soluble We do not eat tributyrin which is a v ry highly artificial fat and I think the explanation is that one is water soluble whereas the usual fats consum d are in fact not water soluble

PROFESSOR HARRISON: I do not know the an wer to the particular vessel mentioned but in the exp rim ntal work whi h ha been done on this nearly all points to the localizing factor being a local stretching stress on the wall I think that is the n arest quick answer I can give

DR TAYLOR: Can Dr Popjak explain from the metabolic point of view the striking predilection for thi disease in the male sex in humans? An incidence which is inci entally not borne ut in experimentally prod iced atheroma in animals

DR POPJAK: I cannot Sir Dr Oliver is going to deal with that problem in detail tomorrow anyway

SIR HOWARD FLOREY: I did m ntion that there are quite a numb r of exp riments which show that if you damage arteries then it is very easy to make lipids a cumulate in them I om tt d s me work of Waters which is a propo in this onne tion and that is if you give allylamine to dogs you can damag their coronary arteries and if you then give th m rath r high dose of variou form of lipids you can g t lesions which look extr mely like atheroma o that I should ay lo alisation in the la t analysis is probably a sociat d with some local damage

PRESIDENT: W have had a number of interesting qu stions asked and if people have afterthought and wi hed th y ł ad a ked some-thing else they can do so in the intervals of lun h t a and coffee

Formation of Artificial Thrombi in Vitro

J C F POOLE

The original users of the Old English word "clott" seem to have meant much the same thing as did the ancient Greeks when they used the word "thrombos " At the present day however the word clot is used to describe the structure formed when blood solidifies in a glass test-tube or some such container and the word thrombus to describe a lump formed by the deposition on the inside of the wall of a blood-vessel of solid

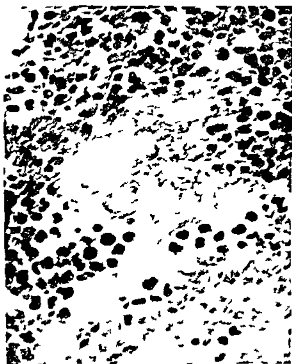


Figure 1 A natur l thrombus H a d E x 1100

material derived from the blood There is of course an inter mediate category of natural and artificial phenomena for which neither word is really appropriate For example when blood escapes from cut vessels and solidifies in a wound what should one call the solid material which is formed? Again when blood is defibrinated by stirring it with a bunch of twigs or some modern equivalent to a bunch of twigs how should one describe the material which sticks to the twigs Fairly soon there may be a need for a new set of words to describe this whole range of objects composed of fibrin and formed elements of the blood but just now it would only add to the existing rather serious confusion to invent new de criptive terms before a little more is known about what one is trying to describe

The important reason for making a distinction between a clot in a test-tube and a thrombus in a blood-vessel is that their microscopical appearances are very different Figure 1 shows a section through a typical natural thrombus which has a very elaborate structure with a complicated arrangement of rounded masses of platelet material forming a sort of loose coralline structure The platelet masses are surrounded by leu ocytes and fibrin and the interstices in the structure are filled with red cells and more fibrin

Figure 2 shows a section through a blood-clot the appear ance of which is quite different All the blood cells including the platelets are distributed at random and none are agglutinated

In practice the structure of a thrombus is often more complicated still A thrombus in the body may consist of two fairly well demarcated regi ns usually known as the white head and the red tail of the thrombus The "white head in such ca es has the structure just described with an elaborate arrangement of ma ses of platelets fringed by leucocytes while the red tail is made up of fibrin and red cells with a few scattered leucocytes Thus the structure of the red tail is not unlike the structure of blood clot but they are not quite the same

Because of the morphological differences between a clot and a thrombus it is obvious that studies of the mechanism of blood coagulation can at the best only help in the understanding of part of the m chanism of thrombosis and clearly there can be no gu rantee that factors affecting clotting will also affect thrombosis nor can it be assumed that factors which do not influence clotting cannot have any influence on thrombosis Consequently there exists at the moment a very real n ed for experimental systems which will help to bridge the very considerable gap in knowledge between clotting in a

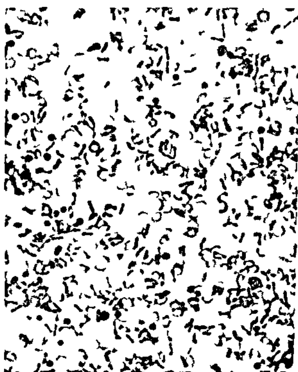


Figure 2 A blood clot H and E x 1100

test-tube on the one hand and thrombosis in a blood-vessel on the other In other words what is needed is an in-vitro system which leads to the production of objects which have the morphological structure of a thrombus but are produced outside the body Several such methods have been devised in the past but will not be reviewed here The experimental results described in this communication were obtained by using a modification of the technique described by Chandler (1958) *

Chandler took a closed circular loop of plastic tubing partly filled with blood and mounted it on a rotating turntable so that the blood was made in effect to flow round and round the closed loop He found that when the blood eventually solidified part of the solid material had the histological structure of a thrombus Chandler s observations were confirmed It was also found that by taking great care over joining the

* Chandler A B (1958) Lab Invest 7 110

ends of the loop of plastic tubing together so as to produce a really smooth joint something is produced which resembles a natural thrombus in its microscopical structure even more closely The apparatus used in these studies is shown in Figure 3 Under these circumstances the blood does not clot

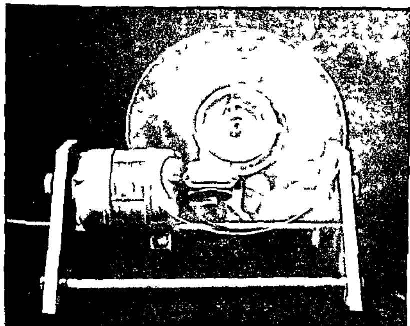


Figure 3 Th appa atu used in th s xpe ment

at all in the ordinary sense that is to say it never solidifies completely Instead a small solid body forms just behind the advancing edge of the column of blood and floats round with the blood for an indefinite period This body when taken out and cut into sections is found to have a histological structure very similar to that of a natural thrombus Figure 4 shows a very low power view of a section through one of these artificial thrombi The white head in the upper part of the field is made up of rounded masses of platelets and leucocytes with red cells and fibrin in the interstices of the structure In the



Figure 4 Low power view of a section through part of an artificial thrombus showing the 'white head (above) and part of the red tail (below) H and E x 45

lower part of the field is part of the red tail which is mainly composed of red cells and fibrin No details of the cellular composition can be made out at this magnification but in Figure 5 part of the "white head is shown in an ordinary low power view and is seen to consist of platelet masses fringed by leucocytes with areas containing red cells between them while Figure 6 shows a more highly magnified field from a similar section A comparison of Figure 6 with Figures 1 and 2 (all three figures are at the same magnification) shows the similarity of these bodies to a natural thrombus and their difference from a blood clot

Because this technique produces something which has a structure similar to that of a natural thrombus it is reasonable to suppose that the sequence of events leading up to the formation of one of these artificial thrombi is similar to the

sequence of events in natural thrombosis and that it might be interesting to know how these artificial thrombi are built up The appearance of fields such as are shown in Figures 5 and 6 suggests that the white head might have been built up by the coalescence of a number of smaller roughly globular bodies That this is so can be confirmed as follows If the blood is allowed to flow round the loop of plastic tubing for about a minute only and is then poured into a glass test-tube it clots rapidly and on sectioning the clot individual platelet and leucocyte clumps are found imbedded in it (Figure 7) These primary clumps later stick together in small groups (Figure 8) and by the end of about two minutes all the primary clumps have united to form a single structure which is the "white head" of the artificial thrombus No further change takes place for several minutes more and then quite suddenly the red tail" forms It seems to be complete in a matter of seconds and no obvious change takes place afterwards



Figure 5 Part of th 'whit head of an artificial thrombu H and E x 260

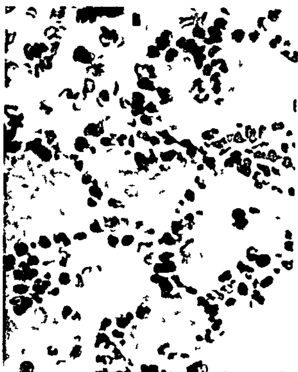


Figure 6 A mor highly magnified view of part of a fi ld imil r to f g 4 x 1100

Another method of observing the early stages in the forma tion of these artificial thrombi has certain advantages Instead of whole blood cell-rich plasma can be used This is obtained by allowing citrated blood to sediment and pipetting off the supernatant plasma which contains nearly all the platelets and leucocytes but very few red cells In experiments with whole blood it was found that there was no obvious difference between using freshly drawn blood and using citrated blood to which calcium chloride solution was added at the beginning of the experiment By using recalcified citrated cell rich plasma instead of whole blood an artificial thrombus is formed which macroscopically and microscopically is similar to one obtained with whole blood except that instead of a "red tail formed from fibrin an red cells there is a tail formed of fibrin only The primary clumps of platelets and leucocytes appear

in the same way as with whole blood and later stick together to form a white head very like that which is obtained with whole blood The use of cell rich plasma has two advantages First the preparation is sufficiently transparent for it to be possible to see the artificial thrombus growing Second the early stages can be studied in film preparations Instead of pouring the contents of the plastic tube into a test-tube and letting it clot as a solid lump it can be poured over a glass slide and allowed to clot as a thin film which can be stained as if it were a blood film Figure 8 is a low power view of one of these film preparations showing three of the primary clumps

Figures 9 and 10 show single primary clumps at a higher magnification They clearly consist of platelets and leucocytes



F gu 7 A primary lump of pl t l ts and leu o yte mbedd d n blood clot H and E x 1500

By examining many clumps such as these it has been possible to show that they consist of platelets, polymorphs and monocytes but do not contain lymphocytes or red cells It would be very interesting to know what property platelets polymorphs and monocytes possess that lymphocytes and red cells do not A systematic study of the behaviour of other types of cell in this experimental system might be rewarding In this connexion

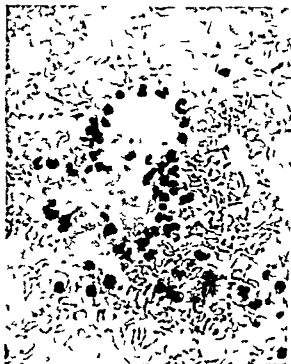


Figure 8 The structure formed by the coalescence and partial fusion of a number of primary clumps imbedd d in blood clot H and E x 1100

a few preliminary observations have been made on the incorporation of bacteria in these artificial thrombi and indeed the part played by bacteria in thrombosis may be of more than academic interest Some bacteria are incorporated in the "white head of an artificial thrombus while others are not To study the incorporation one can use a heavy suspension of bacteria so

that there are enough to show up in a section Figure 11 illustrates the incorporation of Staphylococcus aureus in the same region as the leucocyte fringe around the platelet masses Alternatively one can use smaller numbers of bacteria and incubate the specimen so that small colonies grow where each bacterial cell was lodged Figure 12 shows a colony of Streptococcus pyogenes again at the edge of a platelet mass



Figure 9 Low power view of part of a film p paration of clump of plat lets and leucocyt Lei hman tain x 230

Thus the stages in the formation of these artificial thrombi are as follows Firstly clumps of platelets surrounded by polymorphs and monocytes develop Secondly these clumps stick together to form a single loosely packed body which may be provisionally called the "white head of the artificial thrombus Thirdly a red tail" of fibrin and red cells appears

which surrounds the "white head" fills the interstices in it and streams out behind it Two events in this sequence can be tim d with reasonable precision These are (1) the first



Figure 10 Single clumps of platelets and leucocytes in a film preparation Leishm n stain x 1100

appearance of the platelet and leucocyte clumps and (2) t e first appearance of fibrin For normal human blood clumping occurs at about 1 minute and fibrin formation at about 5 minutes These times under certain circumstances can vary independently

as has been shown by a study of anticoagulants on the process Two different anticoagulant procedures have been studied heparin was added to blood or plasma in vitro and blood was



F gure 11 Singl clump of plat let and l ucocyt s in a f lm p paration Lei hman s tain x 1100

obtained from rats which had been given large doses of vitamin A to produce a prothrombin deficiency In both cases the findings were similar fibrin formation was delayed or suppressed com-

pletely depending on the magnitude of the anticoagulant effect but cellular clumping was completely unaffected The primary clumps of platelets and leucocytes appeared at the normal time and went on to form a "white head of normal structure It



Figu 12 Incorporation of Staphylococcu aureu in the white he d of an a tificial thrombus Gram s stain x 1440

may prove useful to take information of this kind into consideration in assessing the probable effects of anticoagulant treatment on thro-bosis in man



F gur 13 A olony of St pt co cu py g n s g ow ng at th dg of a plat l t clump n th white h ad of an a tifi l th mbu H and E x 1300

Acknowledgments

Most of the experimental work described in this communication was demonstrated at a meeting of the Pathological Society of Great Britain and Ireland held in Oxford in January 1959 and was also presented at a Symposium of the Royal Society of Medicine on 29th October 1959 A fuller de cription of this work has been published in the Quarterly Journal of Experimental Physiology I thank the Editors of the Quarterly Journal of Experimental Physiology for kindly permitting the publication of this short account

Thrombosis and Vascular Occlusion in Vivo

G PAYLING WRIGHT

Our knowledge of the incipient and in many respects the most critical phases of thrombosis may with fairness be said to have originated from the studies of Bizzozero (1882) and of Eberth and Schimmelbusch during the eighties of the last century the full account of which the latter recorded in their classical monograph of 1888 All three were pioneers in that they approached the question dynamically abandoning exclusively histological methods and developing an experimental technique which allowed living blood vessels both normal and traumatized to be examined for hours in the field of the microscope In this way they were able to follow hour by hour the changes that took place both in the affected vessel itself and in the blood as it passed the site of injury Their observations which have since been fully confirmed by the objective methods of continuous time-lapse cinematography have since so dominated our ideas on thrombosis that they may with profit be briefly recalled as a starting-point this morning

It is noteworthy in passing that even if their experimental conditions seemed apparently favourable Eberth and Schimmelbusch found it by no means easy to excite local thrombosis But when the technique is successful the first recognizable change is the adherence at the site of injury of any platelets that are drifting past in the almost clear layer of plasma next it In time more platelets from passing blood become added to those already deposited until after an hour or more a finely granular mass of these elements projects irregularly into the lumen of the vessel Often especially when the blood stream is pulsatile or rapid clumps of superficial platelets are torn away soon to be replaced by further depositions of the same kind In this way as is beautifully displayed by cinematography phases of growth and recession of an incipient thrombus quickly follow one another As a rule however particularly in veins where the current is slow and pulseless the aggregation enlarges until the platelet plaque - initially a mural thrombus - comes to close the lum n of the vessel as an occluding thrombus"

and perhaps eventually to extend into some larger vessel as a propagating thrombus"

Although the adhesion of platelets at an injured site is the first recognizable stage in thrombus formation other blood elements soon become incorporated in the growing mass Interlacing strands of fibrin form between the platelet clumps strengthening the mass mechanically and anchoring it more secure ly at its site of origin Leucocytes frequently and red cells less often become trapped in clefts between the finger like outgrowths of platelets as the mass enlarges From the relative proportions of its ingredients - platelets fibrin leucocytes and red cells in descending order - it is readily understandable how the primary or so-called white head of the thrombus should come to possess its distinctive colour

The studies of Eberth and Schimmelbusch opened the way to at least two lines of enquiry that much concern us today Firstly they directed attention to the need to examine those changes in the endothelial lining of the cardiovascular system that promote the deposition of a thrombus Secondly they emphasized the need to know more of the structure and behaviour of platelets and especially of alterations in their surface at the time they adhere to the vessel wall and gradually conglutinate to form a potential nidus for a subsequent large occluding thrombus Although knowledge on both these aspects of thrombosis has increased in recent years it still remains sadly incomplete and is likely to remain fragmentary until experimental pathologists apply appropriate techniques of surface physical chemistry to the problem

Of the grosser lesions of large vessels such as those of atherosclerosis where the intimal coat has suffered grave disruption there is no need here for further comment My remarks will be confin d to some evidence that even with minor injuries - too insignificant to induce any conspicuous changes in the vascular endothelium - alterations may none the less take place in the intima that materially affect its normally blood-element repellant character

It seems possible that some clue to the nature and location of these initiating changes was provided by some observations recorded by Chambers and Zw ifach (1940) some twenty years ago They noticed that if small particles of carbon - much the same size as platelets - were introduced into the circulation any minor injury to the wall of a small vessel led to their adhesion to its surface This attachment took place particularly along the lines of what used to be termed the cement substance that lies between and supposedly holds together the delicate bevelled edges of contiguous endothelial cells It seems that at these

sites some change can take place which perhaps by causing this material to protrude above the surrounding surface perhaps by making it more sticky renders it more able to trap any particles that may be passing in the slowly moving plasmatic film of blood in contact with it

This apparently promising line of investigation on injured vascular intima has since been followed among others by Samuels and Webster (1952) who employed a technique which enabled them to remove intact the endothelial surface of a segment of a large vessel In this way they could study microscopically both the cells themselves and any foreign elements that might have adhered to their surface They found that as a result of some experimental injury even before any discernible morphological changes occurred in the endothelial cells platelets had become adherent to the lines of "cement substance" in the same way as the carbon particles had done in the experiments of Chambers and Zweifach Gradually additional platelets settled near those first trapped and soon afterwards traces of fibrin became recognizable round them Both processes at first tended to extend over the intima along the lines of the intercellular cement

While we still have far to go before we understand fully the nature of the changes in the intimal lining of damaged blood vessels that prepare them for thrombosis it seems that an advance has been made when a recognizable alteration has been localized in the mucopolysaccharide "cement substance" that lies between the endothelial cells and unites them into a continuous tube Should these changes be substantiated by further experiments they would provide a valuable starting point for further practical research

I shall now pass to the platelets and review very briefly a few recent observations that may throw some light on their participation in the formation of a thrombus There is now ample evidence that in many of the circumstances in which thrombosis occurs changes may be detected in these elements which must be regarded as promoting its development In the first place the platelet count in the peripheral blood may rise to double or treble that found in health Secondly the newly emergent platelets which contribute to this rise appear like all blood elements freshly released from the bone marrow to lack some feature in their surface that gives them their normally mutually repellent character These rises in the number and the stickiness of platelets are found very typically during the few days that follow parturition or any major surgical operation - both times and circumstances when thrombosis is notoriously liable to supervene in the veirs of the legs

The behaviour of platelets in the normal circulation long proved very difficult to investigate One can only admire the skill and powers of observation of Osler (1874) and Bizzozero (1882) when they first noticed the presence of platelets in the normally circulating blood and so disposed of the earlier supposition that they were merely artefacts that arose after blood had been shed and allowed to clot In recent times however high speed photography of small translucent blood vessels has made it possible for Witte and Schricker (1958) to amplify these older observations In rapidly streaming blood as Bizzozero recorded platelets are rarely visible for they are hidden within the column of red cells that form the axial stream in such vessels Only when the current is retarded do they emerge from this central core and become recognizable in the film of plasma that lies next the vessel wall But as long as the endothelial cells were undamaged Witte and Schricker never recorded the adherence of any platelet to their surface The platelet and the endothelial cell both retained their mutually rep llent character

The sequence of changes that take place in platelets once they have become adherent to a surface has b en followed by Braunsteiner and his colleagues in Vienna (Braunsteiner Fellinger and Pakesch 1954) When examined immediately after the blood had been collected and fixed in siliconed glass tubes these elements present the typical disc-like character which according to Bessis (1950) and others they possess while in circulation Under these natural conditions however they are thicker than 300 mμ so that it is not possible to employ the electron microscope to disclose their internal structure But soon after they become attached to a wettable surface they flatten and in consequ nce become amenable to electron microscopy Many delicate pseudopodia can be seen to sprout in all directions from their margins so that the formerly discoid platelet now assumes a spider like appearance Soon the intervals between these pseudopodia become occupied by a delicate web-like film of protoplasm which because of its relative translucency has been termed the hyaloplasm Two further developments quickly follow first small granules become visible in the thinning substance of the platelet and are seen to collect more and more in its centre to form the still opaque "pseudonucleus or granulomere and second the protoplasmic film whose outflowing has constituted the hyaloplasm progressively disintegrates freeing small granules that correspond in size with the microsomes of Claude

It seems likely that this dissolution of the hyaloplasm leads to the release of some factor or factors that can promote

coagulation for not only can these possibly microsomal granules recoverable from such platelets by ultracentrifugation be shown to possess the properties of thrombokinase (Braunsteiner 1951) but the residual pseudonuclear remnant becomes rapidly the focus of a radiating arrangement of fibrin crystals

This analysis of the changes undergone by the platelets after their spreading on some surface suggests that their initial adhesion is not primarily dependent upon the coagulation mechanism for as Jurgens (1951) and others have shown it can also take place in the presence of such effective natural anticoagulants as heparin At the same time the prompt formation of a fibrin mantle round the vanished hyaloplasm together with the persistence of the pseudonuclei as retraction centres for the fibrin formed suggests strongly that coagulation must play a material part in the growth and subsequent mechanical strengthening of any large mass of white thrombus

If the same sequence of changes takes place within the blood vessels as occurs during the examination of platelets by electron microscopy it would seem that the successive events in the initiation of an intravascular thrombus can be summarized as follows First is the intimal probably endothelial cell change which as Samuels and Webster have pointed out may be too inconspicuous to be recognized by the usual histological techniques Second comes the adherence of platelets to the intercellular "cement substance" in the length of vessel affected Third is their swelling and the release of thrombokinase following the dissolution of their hyaloplasm Last is the creation of the surrounding envelope of fibrin which is capable not only of holding the platelet remnants more securely together but also of adding to the size of the thrombus by trapping white and red cells in its growing mass

The incentive in experimental pathology is the tracing of the successive links in the often lengthy chain of changes that develop in structures as they become diseased for by so doing it is hoped that some point of weakness may be identified In practice our present knowledge of thrombosis allows us to do little more than try to break the chain that may end in clinically grave sequelae by employing anticoagulants of various kinds By their use we hope to limit the formation of fibrin at critical sites in an early and potentially growing thrombus and permit natural fibrinolysins to bring about the solution of such as has already formed Their rationale seem to depend on the fact that while they cannot prevent the changes in the endothelial cells and platelets that initiate the process of thrombosis they can lessen the amount of fibrin that may subsequently be formed From the practical standpoint it seems

unlikely that any thrombus mass capable of causing serious obstruction in an important vessel can form unless fibrin makes a substantial contribution to its mechanical strength and internal cohesion

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DISCUSSION

PRFSIDFNT: Thank you very m ch Profe sor Payling Wright for giving us a better nderstanding of some of these processes You can see the idea b hind the morning starting with the changes in the vessels and then going on to the actual clotting rocess The subjects of Dr Pool s and Professor I yling Wright s papers are now open for discussion

DR REYNFLL: There is a very widely held vie that a fall in arterial pr ssure will predispose to thrombosis within arteries and if this is true it is a matter of great practical importance to those of i who try to do clini al medicine The only evid nce that it occurs that I have ever heard is in a few isolated case reports of people who have develop d thrombosis on hypotensive therapy Theoretically it is a littl difficult to see is it not? One can ee that if th re is a fall in cardiac output there must be a r duction in volume flow through some arteries and in th s arteri s you must therefore have either a reduction in lum n or a redu tion in velocity of flow the result of either of these things might possibly predi pos to thrombosis But do ven these considerations apply to th coronary and cerebral circuits which are the on s that oncern is most b cause we know that in conditions like experimental oligaemic shock the coronary and er bral flows tend to be conserved at the expen e of oth r cir uits su h as skin miscle and kidneys? I was wondering if either of the speakers could give us any good th oretical reason why a fall in art rial pressure should predi po e to thrombosi and any fa tual evidence that perl ps it does?

PROFFSSOR PAYLING WRIGHT: I am quite ire that Dr Reynoll i right when he says that a fall in the arterial pre ure loe lead to thrombosis in the coronary circuit That I think ha been shown fairly frequently by the ise of hypoten ive drugs It ha also been recorded after injiry where a great fall in arterial blood pres ure has taken pla e I can only suppose that in the case of the cer bral cir ulation a fall of th t kind must produce a slowing in th circulation

PROFFSSOR M MICHAFI: I wonder if I may ask a question? Is th re any vid n e that there is any difference in th thrombo ing process on the venou side as omp ared with th art rial side of the circulation? I mention this becau e not very long ago we had a clinical pathological confer nce on a pati nt ho had thrombo-phlebitis migrans as a onsequ nce of carcinoma of the pancreas and although there was an enormous amount of v nous thrombo is going on that particular patient who had lots of atheroma and narrowing of his coronary arteries how d nothing whatsoever going on on the arteri l si e ow I wond r why the difference?

PROFESSOR PAYLING WRIGHT: I h ve no suggestion to off r It is an intere ting ob ervation this a sociation between pri r ati tumours and thrombosis and I should have tho ght it one th t

might be followed up but I can offer no solution to this particular question So far as I know there is no differen e in the mechanism of the two Experiments show that th development of these finger-like processes in damaged walls of arteries and veins appear to follow exactly th same our e

PROFESSOR CRAWFORD: It has been shown by a b autiful techniqu that one of Professor Duguid s assistants used that venous en lothelium i a much more potent producer of fibrinolytic substances And it may be that in such an observation as Professor McMichael mentioned there was a failure of the venous fibrinolytic mechanism

DR PAYLISS: Could I ask Dr Poole if he studi d where th fat goes in his experimental thrombi? Is ther any aggregation of lipids in any particular part of his clots?

DR POOLE: No I have not done that yet It is on of th large number of exp riments that I am hoping to do in the n ar future That is obviou ly an important point worthy of investigation

PRESIDENT: This morning has been largely a morning of the exp rimental pathologi t and thi aft rnoon will be very considerably an aftern oon for the clinician b t I hope that we are both interest l in ea h oth r way of thought

CEREBRAL VASCULAR DISEASE

Chairman—J St C Elkington

Extracranial Arterial Disease

E C HUTCHINSON

This communication is devoted to the clinical aspects of cerebral ischaemia resulting from extracranial arterial disease and by extracranial is meant those portions of the carotid and vertebral arteries which lie between the mediastinum and the dura The clinical material is drawn in the main from a series of 100 patients who came to post mortem in circumstances where it was thought that cerebral ischaemia was directly responsible for death or played a part in the final illness The investigation was carried out in conjunction with a colleague Dr Yates and we have already described the methods of examining the brain and the vascular tree (Hutchinson and Yates 1956 and 1957) The method involves injection of the brain with a radio opaque substance through the vessels in the neck and then the later removal of the cervical spine with the carotid and vertebral arteries in situ - a technique which permits detailed dissection

The terms occlusion and stenosis of vessels will be used when referring to extracranial arterial disease Occlusion is of course self-explanatory By stenosis will always be meant reduction of the cross-sectional area of the lumen of the vessel by one half or more

In the patients examined at post mortem disease of th carotid and the vertebral arteries was encountered twice as often as disease of the intracerebral vessels One third of the patients coming to post mortem died as a direct result of cerebral infarction and in only one half of these w s an occluded vessel found within the skull In the other half stenosis or occlusion of either the carotid and the vertebral arteries was responsible

Where the atheroma was confined to the carotid system alone only a third of the patients developed infarction of the brain This is not surprising since surgeons have been ligating the carotid artery with relative impunity for over a century In fact our patients often showed at post mortem an extension of the thrombosis from the carotid artery in the neck directly into the middle cerebral artery within the skull - thus closely

simulating middle cerebral thrombosis Further clinical difficulties may arise when the infarcted brain becomes so oedematous as to cause a rise of intracranial pressure (Clarke and Harris 1958) The papilloedema which may develop under these circumstances coupled with the focal signs of a vascular lesion, makes the differentiation from intracranial tumour difficult without angiography

The most common arterial lesion was stenosis or occlusion of both the carotid and the vertebral arteries and it is in this group that the typical history implicit in the diagnosis of internal carotid thrombosis was encountered If against the background of a progressive neurological lesion the history of staccato short-lived episodes is coupled with monocular impairment of vision and diminished carotid pulsation or a systolic bruit in the neck then the diagnosis of carotid artery disease hardly needs the confirmation of angiography But often the clinical diagnosis is by no means so easy Mental changes for example may dominate the clinical picture from beginning to end Perhaps too the available history may not emphasise the intermittent nature of the symptoms so that the clinical picture may be one of a steadily progressive lesion of one or other cerebral hemisphere and ocular symptoms or abnormality in the cervical vessels to palpation or to auscultation may be lacking In these circumstances angiography is essential to demonstrate the true nature of the underlying lesion

We know that stenosis of the carotid and vertebral arteries may be present without symptoms provided that the mean arterial blood pressure is adequate to maintain the cerebral blood flow However any clinical episode leading to sudden hypotension may dramatically reveal the presence of such a lesion The hypotension may have any cause and haematemesis coronary occlusion and post-operative shock were all encountered at different times Either the patient may unexpectedly lose consciousness and die in coma following the episode of hypotension or if he survives transient or permanent neurological signs may be apparent The pattern of infarction of the brain in the fatal cases may be quite characteristic with symmetrical cerebellar infarcts occurring in association with infarcts of the cerebral hemispheres

The vertebral artery through the basilar and posterior cerebral arteries supplies the occipital lobes the cerebellum and the brain stem In this series occlusion within the vertebral arterial system occurred three times more frequently in the neck than in its branches within the skull In 2 of the 7 cases where vertebral artery occlusion was the sole manifes-

tation of cerebral vascular disease the brain was infarcted in an area ultimately dependent upon the vertebral supply A further 14 cases have been gathered either from personal records from colleagues or from the literature (Adams 1954 Duffy and Jacobs 1958) In all a total of 16 patients each of whom came to post mortem with areas of infarction in the occipital lobes the cerebellum and the brain stem caused by occlusion of the vertebral artery

The ischaemia so produced leads to two characteristic clinical syndromes one difficult and one relatively easy to diagnose The distinction between the two is made on the basis of clinical histories The first group contains those patients who presented with an acute neurological lesion and died in their first illness and the second those patients who experienced transient neurological episodes prior to the final fatal illness There were 7 patients in the first group and 5 died in coma in the first 24 hours The other 2 survived in coma for 4 days and 2 weeks respectively Seen in coma for the first time it is difficult to differentiate the lesion from any other form of acute cerebral vascular disease but the loss of consciousness may be slow in developing and in these a diagnosis of brain stem ischaemia may be relatively easy

An example typical of this group is a man of 69 who was admitted to hospital with vertigo and vomiting of sudden onset There was a low but steady deterioration in his condition over four days and on admission to hospital drowsiness dysphagia and dysarthria were prominent signs Examination of the central nervous system revealed a well marked nystagmus left facial weakness and a left sided Horner s syndrome These signs were noted together with bilateral extensor plantar responses and a blood pressure of 150/100 completed the clinical abnormalities The patient died in coma the day after admission At post mortem there was an infarction of the medulla and also ischaemic areas throughout the pons In the left cerebellum there was an infarct at the junction of the territories of the posterior inferior cerebellar and superior cerebellar arteries The left vertebral artery was occluded within the vertebral canal at the level of the 4th cervical vertebra and equally important was the fact that the left vertebral artery was two and a half times the size of the right The rest of the cerebral vascular tree was free of any significant arterial disease

There were 9 patients in the second group who gave a history of neurological symptoms prior to the final fatal episode In 2 patients the hemiplegia occurred 4 years previously and recovered completely but in the remaining patients these episodes occurred over a period of 12 months prior to death

As one might anticipate from the anatomical origin of these symptoms there was no single clinical pattern Unilateral sensory disturbances were noted vertigo ataxia of the limbs, drowsiness and confusion were all present at different times but in the main these episodes were short-lived and left no residual signs In the patient described by Adams (1954) the episodes occurred at least fifty times before death and often as frequently as three times a day Disturbances of vision were noted in these patients but it was difficult to be sure whether these disturbances originated in the brain stem or in the occipital cortex The difficulties arose from the fact that by chance those complaining of disturbances of vision were unable to cooperate to a degree which would make assessment of the visual fields possible It is only mentioned here since one wonders in view of the fact that three of these cases showed occipital infarction at the post mortem whether or not when a final clinical picture is drawn the syndrome of bilateral occlusion of the posterior cerebral arteries may not be included within it as Symonds and Mackenzie (1957) have suggested

The various symptoms and signs which were encountered in the final episodes in these 16 patients are given (Table I)

Table I

Symptoms and Signs in 16 Patients

Presenting in coma	5
Pyramidal signs (Bilateral in 10)	16
Ocular signs	9
Unequal pupils 3	
6th nerve palsy 1	
3rd nerve palsy 1	
Nystagmus 4	
Dysarthria	7
Dysphagia	6
Facial palsy (? Nuclear in 3)	6
Sensory loss (Either unilateral or bilateral)	4
Vertigo (+ vomiting)	4
Deafness (Unilateral)	2
Palatal palsy	1
Horner s syndrome	1
Mental confusion	2

The lengthy list contributes nothing to the clinical diagnosis but does serve to emphasise the wide variation in the signs which may be encountered and as always the combination of a cranial nerve lesion coupled with long tract involvement is characteristic of any brain stem lesion Attention is drawn to the frequency of the ocular abnormalities the frequency of dysarthria and dysphagia and to the fact that involvement of the pyramidal pathways either unilateral but most frequently bilateral was present in every case

A typical example of this group with an intermittent history before the final illness is a man of 57 years of age admitted to hospital complaining of headaches drowsiness and vomiting of four days duration He had been operated on in 1945 for a mastoid infection and remained well until 1957 when he first complained of a tacks of vertigo Despite the previous history no adequate aural cause could be found for these attacks Suddenly in June 1959 one of his many attacks of vertigo and vomiting was accompanied by severe bifrontal headache and he became drowsy and confused over a period of 48 hours and was then admitted to hospital On admission in addition to drowsiness and mental confusion he was found to be mute Unequal pupils were present together with a left facial palsy and a right hemiplegia and a right sided sensory loss The precise details of the sensory impairment could not be assessed in view of the patient s inadequate cooperation He remained in this state with minor fluctuations of consciousness for nearly two and a half months before he died The essential findings at post mortem were that there were bilateral occipital infarcts in the calcarine fissure estimated to be of between two and three months duration but in addition to this there were bilateral cerebellar infarcts in the distribution of the superior cerebellar artery Examination of the vascular tree showed that there was some degree of atheroma in the internal carotid arteries but this was not encroaching to any significant degree on the lumen of the vessel The posterior communicating arteries in this patient were extremely small a point worth noting since such an anatomical variant may well have an important part to play in the pathogenesis of this syndrome in certain patients The left vertebral artery the smaller of the two showed stenosis at the level of the third cervical vertebra within the vertebral canal and at the same level the right vertebral artery the larger of the two was also occluded by an atheromatous plaque

With one exception the disease affecting the vertebral artery was atheroma and thrombosis The exception was a case where changes in the artery were due to giant cell arteritis

with the typical changes present in both the vertebral arteries and the left temporal artery It is now well recognised that the vertebral arteries are rarely equal in size In this series the disease was bilateral in 2 patients but in 9 of the remainder it was the larger vertebral artery that was occluded by atheroma illustrating the important effect that such an anatomical variation may have

The syndromes we have discussed following occlusion of the vertebral artery in the neck are of course very similar to those of basilar artery stenosis and occlusion as they were defined by Kubik and Adams (1946) Denny-Brown (1953) and Millikan and Siekert (1955) This is only natural since both arteries ultimately supply the same territory in the brain However these results show that vertebral artery occlusion is a good deal more common than the syndrome of basilar artery occlusion and also more common than the classical picture of posterior inferior cerebellar artery thrombosis

There is one set of circumstances where the differentiation between basilar artery and vertebral artery stenosis or occlusion may reasonably be made Recently attention has been paid to the neurological effects of occlusion of the major vessels of the aortic arch We are here only concerned with the subclavian artery from which the vertebral artery usually takes its origin It is interesting to note that the patient described by Broadbent in 1875 under the heading of Absence of pulsation in both radial arteries the vessels being full of blood showed an anomalous origin of the vertebral artery the vessel taking origin from the aortic arch In 5 cases of subclavian arterial stenosis and occlusion recently observed 3 developed a sudden intracerebral lesion In 2 of these the clinical picture had all the hall-marks of a brain stem lesion and the fact that this brain stem lesion was caused by occlusion of the vertebral artery in association with disease of the subclavian artery has already been confirmed in one patient by post mortem The combination of arterial insufficiency in an upper limb and a brain stem vascular lesion produces of course a distinctive clinical picture It is more important to recognise since such a lesion is apparently amenable to surgery

Thus far the discussion has centred round disease of the vessel wall and mention should be made of an uncommon cause of intermittent occlusion of the vertebral artery namely osteo-arthritis of the neuro-central joint of the cervical vertebrae The following patient is of interest in this connection A man of 45 years of age sustained a fracture of the cervical spine in 1957 As a result of his injury he had a spastic weakness of the right arm but no other permanent

neurological signs A year after the fracture, plaster fixation of the cervical spine was removed and from that time onwards he complained of attacks of the following pattern He noted that whenever he extended his head he complained of quite severe pain but whenever he flexed the head his vision became blurred and his legs gave way On examination the findings in the right arm were as noted and with the head in the normal position the ocular movements were full When the head was flexed the patient developed a bilateral 6th nerve palsy and the left plantar response became extensor The neurological abnormalities lasted only a short period of time and then passed off and it was presumed that this clearing of the neurological abnormalities was due to a collateral circulation developing from the carotid vessels through the posterior communicating arteries To appreciate the mechanism here one must remember the normal course of the vertebral arteries and in particular their close relationship to the neuro-central joints De Kleyn (1939) demonstrated that rotation and extension of the head to one side could obstruct the contralateral vertebral artery At post mortem it is possible to show that the distortion of the vertebral artery produced by disease of the neuro-central joint may by movement of the head cause complete obstruction of one or other vertebral artery The x ray of the cervical spine of th patient that we have described shows a considerable bony abnormality in the region of the 5th 6th and 7th cervical vertebrae as an end result of the fracture It seems reasonable to suppose that in this patient there is a marked degree of distortion of the vertebral artery at its point of entry into the vertebral canal and whenever the neck is flexed this degree of distortion is increased to the point of complete obstruction thus producing brain stem ischaemia

Returning finally to the problem of atheroma there is no doubt that the successful surgical attack on the extracranial vascular lesions which has been initiated and maintained in this country by Rob and his colleagues has given a quality of urgency to early diagnosis of these patients Certainly whatever may be the final conclusion as to the aetiology and treatment of athero-sclerosis of extracranial vascular disease the surgical approach would appear to hold ou most promise to this group of patients for the next decade

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Radiological Investigation of Acute Stroke

J W D BULL

One must first attempt to define what is meant by an acute stroke This is not easy but I tentatively suggest the following - "A patient who on clinical evidence has sustained a cerebrovascular accident (including the great vessels of the neck) not due to an aneurysm of arterio-venous malformation "

Over the last two years Dr John Marshall has been investigating an unselected series of acute strokes along these lines We have now partially analysed the findings in the first eighty such cases admitted to his beds in Queen Square These eighty cases will be used as the main basis for discussion since they have the advantage of being serial and unselected

In the radiological investigation four techniques are used and some or all may be necessary in a given case

1 Plain x-rays
2 Angiography
   (a) Carotid right and left
   (b) Vertebral
   (c) Great vessels to include origins of carotid and vertebral arteries
3 Pneumography
4 Positive contrast ventriculography

PLAIN X-RAY EXAMINATION

In practice plain x-rays are seldom helpful but sometimes they provide important clues to the diagnosis and should always be taken

ANGIOGRAPHY

First we must consider the limitations of this method and accept the fact that it is a relatively crude procedure Dr D H Tompsett of the Royal College of Surgeons has prepared beautiful specimens of the cerebral vascular tree by injection of a resin These specimens clearly show the vast vascular network in far greater detail than can be demonstrated by any angiogram It so happens that his specimens are opaque to x-rays and I have had the opportunity of taking radiographs of some of them (Editor s Note Lantern slides were then shown

indicating that radiographs cast shadows of only the larger intra-cerebral arteries - and that an angiogram taken in life reveals considerably less vessels than a radiograph of Tompsett's specimens)

In this series of 80 cases we performed angiograms on them all - 78 carotid and 2 vertebral Table I shows the clinical diagnosis <u>on admission</u> together with the angiographic findings Table II shows the angiographic breakdown In a few cases the

TABLE I

Clinical Diagnosis on Admission	No of clinical diagnoses	Angiographic Diagnoses: Normal	Middle Cerebral	Anterior Cerebral	Int Carotid	Basilar	Haemorrhage	Aneurysm	Failed Angiogram
Mid cerebral occl	41	29	(3)		6		3		
Ant cerebral occl	4	2		(2)					
Int carotid occl	11	6	1		(4)				
Basilar occlusion	4	1				(2)			1
Intracerebral haem	15	7	2		2		(3)	1	
Mid cerebral emb	5	1	(2)		2				
Total	80	46	8	2	14	2	6	1	1

The circles round some of the figures indicate the cases in which the angiographic diagnosis supported the clinical impression

clinical picture progressed making a further angiographic examination necessary and in one case three angiograms were performed over a period of about two years Thus the figures in the two tables are not quite identical

Various points emerged from these tables Firstly the angiograms were grossly abnormal in 40 per cent of the cases and in a further 4 cases the internal carotid artery was pathologically narrow near its origin Secondly middle cerebral occlusion was quite *the commonest clinical diagnosis Thirdly* the clinical diagnosis was often upset by the angiographic findings and fourthly the clinicians usually found themselves unable to differentiate middle cerebral from internal carotid

TABLE II

STROKES

No Abnormality Detected		
Carotid	42)	
Vertebral	1 }	44
Vertebral failed	1)	
Slight Abnormality Detected		
Slight stenosis of internal carotid	4	
Gross Abnormalities		
Internal Carotid - Occlusion	10	
Middle Cerebral - Occlusion	8	
* Haemorrhage intracerebral	8	
Anterior Cerebral - Occlusion		
Basilar - Occlusion or Insufficiency	2	
Anterior and Middle Cerebral - Occlusion	1	
Tumour	1	
Total	80	

One haemorrhage secondary to aneurysm - both demonstrated angiographically

arterial occlusion prior to angiography as Hutchinson and Yates (1957) also found

Analysis of Radiological Findings

No Abnormality Found There were 42 carotid 1 vertebral and 1 failed vertebral angiogram where the findings were negative In my opinion this group may be considered under the following headings -

1 Oc lusion of relatively larger vessels

If angiography was a less crude procedure or if our interpretation was more skilled some of the so-called normals would probably be shown to be abnormal It is quite possible for a large artery particularly one of the primary branches of the middle cerebral artery to be occluded without it being recognized on the angiogram Since the normal arterial pattern varies so much from case to case

it is difficult to state whether a particular artery is absent or has failed to fill, due to occlusion It is even more difficult to detect the occlusion of a small artery or arteries such as those supplying the internal capsule for example

2 Atherosclerosis

It might be thought that by analogy with the great vessels such as the aorta one could recognize athero-sclerosis radiologically by observing (a) increased tor-tuosity (b) variations in calibre of an artery or arteries and (c) local irregularities in the walls We have studied these features objectively and found no correlation between incidence of tortuosity and the known presence of cerebro-vascular disease But in the case of calibre variation and local irregularities in the walls such a positive correla tion did exist although of course these features were not confined solely to the stroke cases and were seen to a lesser extent in controls of the same age Thus in isola-tion it cannot be taken as a diagnostic criterion

For the purposes of the present analysis we have only considered those cases as "abnormal" where there was some obvious stenosis of the origin of the internal carotid artery There were four such cases in the series one of which is illustrated in the Demonstration *

3 Intracerebral haemorrhage

One knows from experience gained by surgical colleagues that a normal" angiogram supported even by a normal pneumo-encephalogram does not exclude a quite large intracerebral haematoma McKissock Richardson and Walsh (1959) have recently shown that patients with negative angiograms and ventriculograms may harbour significant intracerebral haematomas Although we are concerned here to-day with occlusive cerebro-vascular disease clini al experience shows that we cannot always differentiate occlusion from haemorrhage This becomes important if anticoagulants are to be prescribed

4 The Thoracic Portion of the Great Vessels

Hutchinson and Yates (1957) focussed attention on the origin of the vertebral arteries where they left the sub-clavian artery at the root of the neck Disease at this site is not easy to demonstrate angiographically and such

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* A demonstration was set up in the College illustrating the various lesions found angiographically

lesions may be present in association with a normal peripheral cerebral arteriogram of the classical type

We have not yet developed an entirely satisfactory radiographic technique for the demonstration of stenosis or occlusion of the mouths of the vertebral arteries As commonly happens in any branch of medicine in such circumstances several methods have been advocated I will briefly mention three of them -

(a) The method of Viallet and his colleagues This consists in a rapid intravenous injection of a large quantity of contrast substance which opacifies all the main vessels of the body It appears to give good results in small children the usual indication being the investigation of congenital heart lesions The method is not n arly so satisfactory in elderly adults and timing of the arrival of the bolus of the contrast substance at the mouths of the vertebral arteries is difficult Unless the timing is accurate the radiograph is valueless

(b) Catheterisation of a variety of arteries has been tried In my opinion none is entirely satisfactory

(c) Retrograde percutaneous subclavian angiography (Morris, 1959) is probably the best method yet devised but it carries the risk of a pneumothorax which is not less than about 10 per cent even in skilled hands

The Grossly Abnormal Angiogram In this group consisting of 32 out of 80 cases (40 per cent) the radiographic appearances were unequivocal

The findings may be summarized as follows - Main vessel occlusions were seen most often The classical sites for the commonest occlusions are (a) about 1 cm from the origin of the internal carotid artery (10 cases not all at the classical site) and (b) about 1 cm from the origin of the middle cerebral artery (8 cases) The trifurcation or bifurcation of the latter vessel is usually about 2-3 cms from its origin varying from patient to patient

Intracerebral haemorrhage was diagnosed in 8 cases Strictly speaking it cannot be differentiated angiographically from oedema or even an avascular tumour mass

Occlusion of the anterior cerebral artery is much more difficult to diagnose partly on account of the variable anatomy of the circle of Willis The same argument applies to the posterior cerebral arteries Our experience shows that neither of these vessels becomes occluded nearly as frequently as the middle cerebral artery

Basilar occlusion was diagnosed twice by carotid angiography in the series The diagnosis was made on the grounds

that the terminal portion of the basilar artery filled spontaneously from the carotid and that an identical appearance was seen on three successive injections Absolute confirmation if required could be obtained by vertebral angiography a procedure we were less anxious to undertake on patients with poor arteries and in Marshall s series we tried as far as possible to limit the angiographic investigation to one main vessel

The possibility of the presence of a cerebral tumour must always be borne in mind Only one was found by angiography in this series an astrocytoma of Grade III malignancy In spite of the fact that this was a carefully studied clinical series we have demonstrated a failure to make the distinction between a stroke and a tumour While it is probable that the clinical presentation was in fact due to a vascular occlusion secondary to a tumour yet the tumour was not detected Nor indeed was it detected at the first angiographic examination performed just after the stroke Deterioration in the patient s condition prompted us to repeat the angiogram seven weeks later by which time the tumour mass and its pathological circulation had become apparent radiographically

Per contra cases diagnosed as tumours are shown at angiography to have no tumour but a major vessel occlusion

PNEUMOGRAPHY

It must be pointed out that in the above series just discussed none of the cases was examined pneumographically since surgical treatment was not contemplated in this group But experience with neurosurgical colleagues particularly in Mr McKissock s series has proved the value of pneumography

Intracerebral Haemorrhage

If in an acute case of stroke the angiogram does not confirm or exclude the presence of an intracerebral haemorrhage pneumography may be necessary The following examples will I hope make the indications more clear -

A Positive Carotid Angiograms may be divided into four groups

1 In this group the site of the haemorrhage is clearly defined angiographically This applies particularly to temporal lobe haemorrhages but also less often to other sites In such cases pneumography is redundant

2 Displacement of midline arteries and veins will indicate swelling of the hemisphere but may give no accurate localising signs Ventriculography will frequently pinpoint the haematoma

3 idening of the so-called "U loop formed by the anterior and middle cerebral arteries in antero-posterior projection suggests haemorrhage or oedema in the region of the basal ganglia but ventriculography may give further and more accurate data

4 The only positive feature may be a wide sweeping of a midline anterior cerebral artery This sugge ts that hydrocephalus is present and that there may be a haemorrhage in the mid brain and/or in the posterior fossa Ventriculography will usually settle the issue

B Negative Carotid Angiogram A haemorrhage particularly parietal may be present Indeed as already mentioned experience with Mr McKissock's large series of cases has shown that sometimes a parietal haemorrhage is present when both the angiogram and pneumogram are negative

C Negative Carotid and Vertebral Angiograms This does not exclude a haemorrhage anywhere in the brain Ventriculography will assist by demonstrating the absence or presence of deformity of the ventricular system

POSITIVE CONTRAST VENTRICULOGRAPHY

This is necessary on the rather infrequent occasions when pneumography gives an equivocal result, particularly with regard to the midbrain and posterior fossa The old maxim that masses in the midbrain or posterior fossa always cause hydrocephalus should be forgotten as it is so often not true When hydrocephalus is absent it is difficult to manipulate enough air into the aqueduct and fourth ventricle to cast an adequate shadow so that these structures may not be delineated In such circumstances about 2 cc of myodil can be introduced via the ventriculographic burr hole into a lateral ventricle the contrast substance being then manipulated under the fluorescent screen into the appropriate ventricular chambers and x-rays are taken By this means midbrain pontine cerebellar hemisphere and vermis haemorrhages may be demonstrated and differentiated from one another

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Treatment of the Acute Stroke
1—Intracerebral Surgery

W McKISSOCK

Over a period of years we have collected a consecutive series of 244 proven cases of primary intracerebral haemorrhage after excluding all cases of such haemorrhage due to trauma, aneurysm angioma or systemic disease We have also excluded those patients with pontine or cerebellar haemorrhages as these two latter conditions present different diagnostic and therapeutic problems

The age incidence is shown in the accompanying table (Table I) and it should be mentioned that the low incidence in the last

TABLE I

Age in years	20-29	30-39	40-49	50-59	60-69	70 & over
Number of cases	6	15	59	90	54	20

two groups is almost certainly due to selection at the level of the admitting hospital, the very elderly probably being thought unsuitable or too ill for transfer and to the rapid death of many patients in their own homes before hospital admission could be arranged

The sexes were equally represented there being 124 males and 120 females Of those upon whom full details concerning the onset were available 58 were active whilst 60 were at rest at the time of ictus

Hypertension was certainly present in 152 patients but equally certainly absent in 57

It is not proposed to enter here into the clinical aspect of the patients save to state that purely clinical diagnosis is not sufficiently accurate and that ancillary methods of investigation are essential if the diagnosis of primary intracerebral haemorrhage is to be relied upon

Of the 244 cases in the series 12 died before surgical treatment could be undertaken leaving 232 patients for consideration

The various methods of surgical treatment employed are shown in Table II

TABLE II

Methods of Surgical Treatment Employed for Primary Intracerebral Haemorrhage	
Ventricular Tapping alone	9
Ventriculography alone	14
Burrhole Exploration and Evacuation of Haematoma	104
Burrhole Aspiration of Haematoma with subsequent Craniotomy	73
Craniotomy for Evacuation of Haematoma	31

The follow-up period varies from 1 - 10 years during which time 31 of the original 102 survivors have died from the causes listed in the next table (Table III)

TABLE III

Results of Surgical Treatment

	No of Patients	Deaths	
Ventricular Tap alone	9	9	
Ventriculography alone	14	11	(two improved but died (later one alive with (moderate disability)
Definitive Surgery	208	106	

Improved by Surgery 14	From further C V A	4
	From other known causes	6
	From unknown causes	4
		14
Unimproved by Surgery 17	From progression of disease in periods of 1-3 months	10
	From further C V A	1
	From other known causes	1
	From unknown causes	5
		17

Eight patients were lost in follow-up so that 63 remain for assessment

Patients were considered to be "well" if they were able to return to full normal employment minimally disabled" if able to do light or part-time work moderately disabled if unemployed and totally disabled" if unable to lead an independent existence Table IV gives the figures for each of these categories

TABLE IV

Well	25
Minimal Disability	14
Moderate Disability	18
Disabled	6
	63

Our interest has naturally been centred on those features which appear to influence the mortality rate and firstly it may be said that age seems to be no bar to surgical treatment apart from those falling into the "70 and over" group (Table V)

TABLE V

Age in Years	20-29	30-39	40-49	50-59	60-69	70 & over
Deaths	3	7	30	53	31	16 - 140
Total Cases	6	15	59	80	54	20 - 244
Mortality % Age	50	45	42	55	57	80

The situation of the haemorrhage however seems to be of great significance for it can be seen from Table VI that the deeply situated disruptive haemorrhages involving the internal capsule basal ganglia and ventricular system even though small in size carry a devastatingly high mortality rate

Hypertension is only significant in that those patients with high blood pressure seem to be particularly prone to suffer capsular haemorrhages for if these be subtracted, the death rate in hypertensive and normotensive groups is the same

The state of consciousness at the time of operation is undoubtedly of great importance We have divided the patients

TABLE VI

	Frontal	Fronto-parietal	Fronto-temporal	Parietal	Parieto temporal	Parieto-occipital	Temporal	Temporo-occipital	Capsular	Hemisphere
Totals	30	17	9	41	19	7	51	3	56	10
Deaths	10	10	3	14	7	7	21	1	52	9
Mortality % Age	33%	59%	33%	34%	37%	100%	41%	33%	93%	90%

into four grades of conscious level - "alert "drowsy stuporose" and "comatose" There were 58 alert" patients with a mortality of 23 per cent 98 drowsy" with a mortality of 46 per cent 32 "stuporose" patients with a mortality of 75 per cent and of the 56 patients in coma all died

We have made an attempt to assess the value of different forms of surgical treatment in relation to the varying degrees of consciousness and again as Table VII shows the death rate

TABLE VII

Burrhole Aspiration Alone			
Alert	24 cases with	5 deaths	- 21%
Drowsy	39 cases with	26 deaths	- 66%
Stuporose	18 cases with	16 deaths	- 90%
Coma	23 cases with	23 deaths	- 100%
Total	104	70	
Craniotomy and Evacuation of Clot			
Alert	13 cases with	0 deaths	- 0%
Drowsy	15 cases with	6 deaths	- 40%
Stuporose	1 case with	1 death	- 100%
Coma	2 cases with	2 deaths	- 100%
Total	31	9	
Burrhole Aspiration followed by Craniotomy			
Alert	16 cases with	3 deaths	- 19%
Drowsy	37 cases with	12 deaths	- 32%
Stuporose	16 cases with	8 deaths	- 50
Coma	4 cases with	4 deaths	- 100%
Total	73	27	

rises with diminishing degrees of conscious level

It will be seen that all forms of surgery in the "stuporose" and "comatose" groups have been singularly unsuccessful but that elective craniotomy would seem the operation of choice in the "alert" patient

A 25 per cent total survival rate after 10 years with but 10 per cent of normal individuals and 5 per cent only minimally disabled may seem a disappointing result but it must be pointed out that no comparable series of cases of proven primary intracerebral haemorrhages treated conservatively exists for comparison We have therefore embarked upon a controlled clinical trial of surgical versus medical methods of treatment which should within a year from the present time provide a statistically significant answer to this pressing problem

form of the arterial lesions in these patients It should be stressed again as Ramsey Hunt did in 1914, that the lesions here are no different from those occurring in the limbs of patients with atherosclerosis and that thrombosis of a large extracranial artery is a common cause of clinical abnormalities in patients with cerebral atherosclerosis

The severity of symptoms in these patients depends upon the efficiency of the collateral circulation through the circle of Willis when this is exceptionally good there may be only minor transitory symptoms from even a bilateral occlusion of the internal carotid arteries From the surgeon's point of view these occlusions may be partial or complete an arterial stenosis or thrombosis The former are relatively easy to treat the latter more difficult Clinically it may be impossible to distinguish between a partial and a complete occlusion Patients with either may have transitory attacks of sensory or motor paralysis followed by complete normality patients with either may develop a complete and permanent hemiplegia Palpation of the carotid pulses is a confusing physical sign and until recently arteriography or surgical exploration has been the only sure method of making the diagnosis In our experience of several thousand patients with occlusive arterial disease arterial auscultation has gradually emerged as a useful physical sign and this is particularly so in patients with stenosis of the carotid or vertebral arteries Arteriography here as elsewhere is not without risk in some patients auscultation makes it unnecessary If one listens with stethoscope over the bifurcation of the common carotid one can hear a systolic murmur in about f
with a stenosis at this site the normal artery and
ly occluded vessel have no such murmur The
external carotid artery with a normal
exhibit a similar murmur and not require
of the origin of the vertebral artery can
same way and in patients with both lesions
locations of the murmurs serve to d
other Today I would be prepared to
graphy on a patient with a murmur in the
taking into account the other clinical fir

It is of interest to speculate as to
vertebral stenosis produces symptoms
illustrating some of the possible ways F
become a complete thrombosis Second
the surface of the plaque of atheroma and
lumen of a stenosed artery but not
complete thrombosis Third a

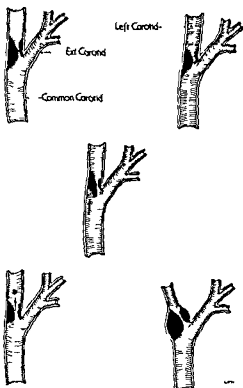


Figure 2 F ve methods by wh ch a stenos s of an nternal carot d artery c n cause symptom A sixth method a change n th general circulat on uch as a fall in th ca d ac output which may r du e further the flow through a t nosed a tery h s not b n illustrated (Rob C G Proc Roy Soc M d 1959 by court y of the Honorary Editors)

plaque of atheroma and lift it up like a flap as the blood clot organises the plaque drops back and the degree of sterosis is reduced Fourth a portion of clot becomes detached from the atheromatous plaque and an embolus results Fifth the artery distal to a stenosis may go into spasm and sixth some general change in the circulation such as a reduction in the cardiac output may reduce further the flow through a previously stenosed artery We have seen definite examples of all these except for the fourth and fifth (Rob 1959)

Surgical Treatment

Previous attempts at the surgical treatment of occlusions of the internal carotid artery have included sympathectomy and arterectomy, both of which had little if any effect on the course of this disease Both the first successful arterial reconstruction operation for this lesion (Eastcott Pickering and Rob

19,4) and the first report of a large series of operations (Rob and Wheeler 1957 Rob, 1959) have been from St Mary's Hospital Our experience as Table I shows is now of more than 106 such operations and it is from this that the following conclusions have been drawn

TABLE I

OPERATIVE RESULTS IN 106 PATIENTS WITH INTERNAL CAROTID ARTERY OCCLUSIONS

Type of occlusion	No of patients	Good flow established	Post-Operative Course				
			Asymptomatic	Objectively better	No change	Temporary deterioration	Died
Partial Hypothermia	84	82	54	15	11	2	2
Normal temp	2	2	1			1	
Complete	20	4	1	1	15		3
TOTALS	106	88	56	16	26	3	5

The first point is that the results of surgery are much better when the occlusion is partial Once the thrombosis has become complete surgery as practised to date can only succeed during the short period before irreversible cerebral damage has occurred or the intracranial portion of the thrombosis has become adherent so that arterial reconstruction is no longer possible This means that clinicians should attempt to diagnose these lesions before a complete thrombosis has occurred (Figure 3) Operation at this stage of arterial stenosis before thrombosis is to a certain extent a prophylactic procedure but this is in line with modern surgical thought on the treatment of atherosclerosis at this and many other sites As the Table shows it is nearly always possible to restore a good lumen to a stenosed internal carotid artery

Another point is the management of a patient with multiple stenoses of say one vertebral and both internal carotid arteries Whilst it is possible to restore a normal flow through each vessel and the theoretical advantages of having the brain supplied by four main arteries instead of three or even two are



F gu e 3 A part al occlusion f the nt rnal a ot d art y du to a plaque of athe oma Note th w dg shaped plaque t th o g n of the nt nal arot d a te y

obvious, it has been our experience that restoration of a normal flow through the carotid arteries is usually sufficient although when a vertebral artery alone is stenosed or the clinical findings indicate vertebral arterial insufficiency then this vessel should be reconstructed

Choice of Operation and Technique

e have found that the best procedure has been a thromboendarterectomy and we have been able to use this operation on more than 90 per cent of our patients The next most satis-

factory has been the excision of the stenosed segment when short and reconstruction with a direct end-to-end anastomosis Only in a small minority has it been necessary to restore continuity with a blood vessel graft or a plastic prosthesis For complete occlusions no special precautions are necessary because the only functioning artery to be clamped will be the external carotid but we find that hypothermia is necessary for the protection of the brain when the artery is only stenosed We cool the patient to 29°C or 30°C and find that this is sufficient It is unusual for the period of arterial occlusion to exceed 20 minutes

Results

Table I gives the early picture but as with all treatments for lesions due to atherosclerosis early good results are not difficult to obtain It is the late picture which counts Fortunately our follow-up conducted by Dr Harold Edwards and Dr Neil Gordon (1959) has shown satisfactory results Our first patient operated on in 1954 at the age of 66 is alive and well aged 71 and this is fortunately the case with the majority including some of those who have had severe neurological abnormalities before operation (Edwards and Rob 1956) The recurrent thrombosis rate has been extremely low for an arterial reconstruction procedure on vessels of this size this point interests me greatly as a surgeon I believe the possible explanations include - the fact that the atheromatous plaques are often well localised that the distal arterial tree may be remarkably normal that the operation is not technically difficult once the initial experience has been gained and that the flow along the internal carotid and vertebral arteries is rapid at all times Post-operative long term anticoagulants have been used in about half the patients I personally favour them the main indication for not using them in this series has been that the physician concerned has held the opposite view

Conclusion

We believe that stenoses of the cervical portions of the internal carotid and vertebral arteries of sufficient severity to be diagnosed clinically should be treated surgically This is to a certain extent a prophylactic procedure

Complete thrombosis of these arteri s could be treated in the same way but it is rare for the diagnosis to be made in time

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Treatment of the Acute Stroke
3—Medical

D A SHAW

The scope of medical treatment of the acute stroke remains confined almost entirely to the general support of the patient through the natural course of his illness The greatest value of the research of recent years in cerebrovascular disease has been its production of an awareness that it is a disease of the young and middle-aged as well as of the elderly the preponderance of the latter has in the past obscured the high numerical incidence in the younger age groups and the high mortality in the elderly has resulted in erroneous impressions of the natural history of the disease Although therefore it cannot be claimed with the support of incontrovertible evidence that any specific form of treatment influences beneficially the outcome of a stroke such attempts as have been made do underline the necessity of applying the general measures available to us with energy and judgment In the acute phase the problems are those common to all unconscious severely ill and incapacitated patients such as the maintenance of fluid balance nutrition and pulmonary ventilation In the recovery phase however there are problems peculiar to the patient who has had a stroke and a dynamic approach to rehabilitation may greatly influence the final degree of functional recovery

Turning to specific treatments which aim to modify the intracranial lesion itself or its immediate effects on the nervous system I think that the explanation of the almost complete absence of success lies in the lack of fundamental knowledge which is necessary to all rational hypothesis Many of the problems are of course common to the whole field of vascular disease but we are dealing with a peculiarly complex vascular system which is not readily amenable to physiological experimentation in man and we are particularly handicapped by the lack of a convenient method of measuring cerebral blood flow Our theories of the pathogenesis of cerebrovascular disorder are highly speculative in many instances and our inability to correlate clinical manifestations with pathological processes renders all therapy somewhat empirical Perhaps the

most outstanding weakness is our clinical inability to distinguish with certainty two such grossly different pathologies as infarction and haemorrhage and it is for this reason that terms as unscientific as stroke " continue to be used

As we are at present concerned with occlusive vascular disease it is proposed to discuss only those specific forms of treatment which have been applied to clinical "strokes" which we believe to be due to cerebral infarction The first of these to gain any prominence was stellate ganglion block introduced by Leriche and Fontaine in 1934 Although they and others subsequently reported striking benefit from this procedure it was shown by Scheinberg (1950) that successful bilateral stellate block does not produce any change in cerebral blood flow or cerebral vascular resistance

Many vasodilator drugs have been used with the aim of increasing cerebral blood flow but with the probable exception of papaverine they are ineffective Some although producing cerebral vasodilatation fail to affect blood flow because of a coincidental hypotensive effect The most effective means of increasing cerebral blood flow is the inhalation of 5 to 7 per cent carbon dioxide but as Kety (1954) has suggested a high tension of carbon dioxide must already result from the ischaemia associated with acute infarction

Cortico-steroid therapy has been advocated by Russek Russek and Zohman (1955) on the basis that it may inhibit cellular reaction and thus reduce the cerebral oedema associated with infarction However it is difficult to draw firm conclusions from their uncontrolled series of thirty-five patients It is not possible yet to make any assessment of the value of fibrinolytic enzymes which are still in the experimental stage in cerebrovascular occlusion

The establishment of the place of anticoagulant drugs in the treatment of myocardial infarction has raised the question as to their possible value in cerebral infarction and I think that it is to this form of therapy in particular that physicians have looked with some hope Even in coronary disease these drugs have shown a singular reluctance to yield to clinical appraisal and our task is made particularly difficult in cerebrovascular disease by the diagnostic and prognostic uncertainties already referred to Many reports have been published particularly in the United States on the use of anticoagulants in cerebrovascular disease in many instances these have been favourable particularly with regard to carotid and vertebro-basilar disease In this country Carter (1957 1959) has reported beneficial effects in embolic infarction and also in non-embolic infarction

of gradual development He did not encounter the conversion of white to red infarcts, under the influence of anticoagulants that had been regarded as a serious hazard and that animal experiment had forecast

In view of the difficulty of assessing therapeutic results in a condition of such unpredictable pattern it was felt that anticoagulants should be tested on the basis of a strictly controlled clinical trial and I wish to present the results of such a trial recently undertaken It was decided to restrict the trial to patients believed to be suffering from strokes" due to non-embolic infarction as it is considered that embolic infarction presents a separate problem in that the cerebrovascular tree need not necessarily itself be inherently diseased Furthermore it was decided to include the whole range of cases commonly encountered in general medical practice rather than to restrict the trial to subgroups in which diagnostic distinction is so often uncertain

Trial procedure

The primary objective of the trial was to assess the influence of anticoagulants on the immediate mortality but in addition any possible effects on late mortality or subsequent recurrence were sought All patients admitted to the trial were under 70 years of age We aimed to start treatment as soon as possible after the onset of the attack but 72 hours was the maximum interval permitted Following admission to hospital a diagnosis was reached on the basis of history and physical examination lumbar puncture principally to determine the presence or absence of blood in the spinal fluid and cerebral angiography of the appropriate vessel Patients who were found to have blood in the spinal fluid were obviously excluded from the trial as were those with severe hypertensive retinopathy or left ventricular failure the latter because their condition might demand the use of hypotensive therapy Peptic ulceration or evidence of bleeding disease were likewise regarded as contraindications

Patients accepted for the trial on the basis of these criteria were then allotted by a randomisation table to one of two groups, those to receive anticoagulant therapy and those to act as controls Obviously the decision whether or not to include them in the trial was taken without knowledge of the group to which they would be allotted They were randomised in pairs but were not differentiated by sex and no attempt was made to match them on the basis of any particular feature of their disease

The treated patients received an initial dose of 300 mgms phenindione (Dindevan) and, starting twelve hours after their

angiogram they were given three doses of Heparin (12 500 units) intravenously at six-hourly intervals We have found that earlier administration of Heparin is liable to result in bleeding from the site of arterial puncture From the second day onwards the dose of phenindione was regulated by daily prothrombin estimations using the Quick one-stage test the prothrombin time being maintained between two and three times the control Treatment was continued for three weeks and then gradually withdrawn There was uniformity in the nursing and physiotherapy in both treated and control groups This is considered to be of great importance in a condition where such complications as respiratory obstruction pulmonary infection and electrolyte imbalance can influence the mortality to a marked extent

Case material

Fifty-one patients were admitted to the trial 26 in the treatment group and 25 in the control They included 24 males and 27 females with approximately even distribution of the sexes to the two groups Table I shows the age distribution in decades It will be seen that 14 out of the total of 51 were below the age of fifty The diagnoses based on clinical and angiographic findings are given in Table II Ten patients had

TABLE I

AGE DISTRIBUTION

AGE	TREATMENT	CONTROL	TOTAL
30-39	2	2	4
40-49	7	3	10
50-59	13	9	22
60 69	4	11	15
TOTAL	26	25	51

TABLE II

DIAGNOSIS

SITE OF OCCLUSION	TREATMENT	CONTROL	TOTAL
MIDDLE/ANTERIOR CEREBRAL	19	17	36
VERTEBRO-BASILAR	3	4	7
INTERNAL CAROTID	4	4	8
TOTAL	26	25	51

mean diastolic pressures of 110 mm Hg or above 4 in the treatment group and 6 in the control

Results

Because of the differing opinions and the conflicting evidence both with regard to the efficacy and the hazard of this form of treatment it was desirable that results should be subject to continuous analysis as they became available so that the trial might be concluded as soon as a result was achieved Classical significance tests are, of course, inapplicable when a trial is analysed in this way and therefore it was decided to adopt a sequential procedure We are indebted to Dr Armitage for the statistical design of the trial which is embodied in the sequential chart (Figure I) showing the results

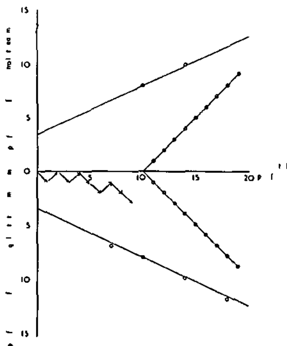


Figure 1

As mentioned already patients were randomised in such a way that each was paired with another patient in the opposite group The present form of analysis takes cognizance of the behaviour of pairs and it is only when their behaviour differs that progress of the trial is recorded That is to say that if both members of a pair survive or both members die and six weeks was taken as the period of observation for this assessment no preference for treatment or control is revealed and no progress is therefore plotted These are referred to as tied pairs If on the other hand members of a pair behave dissimilarly (untied pairs) then a preference is indicated either for treatment or control according as to which member survives

In this particular chart the number of untied pairs is marked on the abscissa and the ordinate represents the number of preferences for treatm nt minus the preferences for control Positive values thus indicate the sum preponderance of treatment preferences and minus values the number of control preferences The progress of the plot is observed until one of the boundaries is reached Reaching the upper boundary indicates a definite preference for treatment and reaching the lower boundary a definite preference for control f either of the two middle boundaries is reached then no significant difference exists between treatment and control

In this instance the boundaries were set to allow the detection of a 17 per cent difference between the mortality rates in the two groups at a probability value of 0 97 That is to say that if a difference of 17 per cent between the mortality rates in the two groups existed one would expect to detect this difference on ninety-seven occasions out of a hundred The design of the trial was such that the probability of the result obtained be it positive or negative occurring by chance was less than 5 per cent

The progress of the trial as indicated by the arrows clearly shows a trend unfavourable to the anticoagulant treated group A point was reached when the upper boundary was unattainable and even had the next two untied pairs shown preference for anticoagulant therapy the conclusion would have been that no significant difference existed between treatment and control The trial was therefore suspended at this stage

Table III shows a summary of results in orthodox form No conclusions can be drawn with regard to late deaths or incidence of further ischaemic episodes Postmor em examinations were performed on all the patients who died within the first six weeks and among those who had been in the treated group there were three who showed evidence of intracerebral

TABLE III

SUMMARY OF RESULTS

	TREATMENT	CONTROL
EARLY - within 6 weeks		
DEATHS	6	3
FURTHER ISCHAEMIC EPISODES	0	2
LATE - 6 weeks to 6 months		
DEATHS	2	4
FURTHER ISCHAEMIC EPISODES	3	0

haemorrhage Our interpretation of this finding is that the presenting stroke in these patients was attributable to haemorrhage and not to infarction and that the correct pathological diagnosis was not made in spite of the inclusion of lumbar puncture and cerebral angiography in the initial investigation

Our conclusion is therefore that used in accordance with our criteria of selection and management anticoagulant therapy is not indicated in patients who have suffered a stroke e believe that the criteria chosen are those most readily applicable to general medical practice

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Present Management of Cerebral Vascular Disease

J MARSHALL

The cerebrovascular part of this symposium has been largely devoted to the diagnosis and treatment of the acute stroke Therefore despite the fact that the title of my contribution is a wide one I propose to devote myself to the long-term management of the patient with cerebrovascular disease Moreover as time is limited I further propose to concentrate on two main aspects the use of hypotensive drugs and the use of anti-coagulant therapy

I do not think it is sufficiently appreciated how great are the uncertainties with regard to the diagnosis and treatment of cerebrovascular disease The clinical picture of cerebral infarction may be due to embolism from the classical extra-cranial sites or possibly from thrombi developing upon athero-sclerotic plaques in the great vessels of the neck It may be due to thrombosis in the great vessels of the neck or in the intra-cerebral vessels themselves It may be due to so called insufficiency" in which there is a reduction of blood flow through a stenosed but not occluded vessel below the level necessary for the function of cerebral neurones It may also be due to spasm of cerebral vessels as seen for example after rupture of an anterior communicating aneurysm Moreover we know that the clinical picture of cerebral infarction may well be due to small intra cerebral haemorrhages a possibility which adds to the anxieties of those treating this condition Evidence as to what proportion of strokes is due to each of these mechanisms is sadly lacking and our ability to distinguish one from another at the bed side is limited hence preventative measures must be largely empirical rather than rational

The place of hypotensive therapy in cerebrovascular disease is far from clear nor is there much prospect of its being clarified in the near future Hypotensive therapy is so obviously beneficial at least temporarily for malignant hypertension retinal changes and left ventricular failure that a controlled clinical trial was out of the question Furthermore it was irrelevant from the present standpoint

for the greater proportion of such patients die a cardiac or renal death It is in the remainder of hypertensive patients, in whom the possibility of a cerebrovascular death looms larger, that the need for an assessment of the effect of hypotensive therapy on the incidence of further strokes and upon the death rate from cerebrovascular accidents is greatest Conflicting views have been expressed on this point some authors having the impression that the incidence of cerebrovascular accidents is reduced by therapy (Smirk 1957) whereas others feel that cerebrovascular accidents may be precipitated by hypotensive therapy (Locket et al 1951) We know of course that in extreme circumstances either possibility may occur Thus the excessive lowering of blood pressure for neurosurgical intracranial operations has been followed by cerebrovascular catastrophies while it has long been known that hypertensive crises may be associated with transient or even permanent strokes The problem is as to what in the long run over a large series of patients will be the effect of hypotensive therapy on the incidence of further strokes and on the mortality from cerebrovascular accidents To this problem there is no clear cut answer and I think that it is now too late in the day for a controlled clinical trial to be a practical proposition The present position appears therefore to be that hypertension is or is not treated largely on the basis of such indications as the cardiac retinal or renal state of the patient or on the height of the blood pressure in younger men but that the cerebrovascular status has little influence on the decision

The situation with regard to anticoagulant therapy is more satisfactory for though the same problem of pathogenesis and diagnosis confronts us at least we are still in a position to design and execute a controlled clinical trial Previous studies by Millikan Siekert and Whisnant (1958) Fisher (1958) and McDevitt (1958) have suggested that anticoagulant therapy may be of benefit in reducing the incidence of further strokes in patients with cerebrovascular disease This applies especially to those whose lesion is in the brain stem or who are suffering from recurrent episodes In all these studies the control series was not collected in accordance with the strict criteria which I believe to be necessary in a disease which is so variable in its clinical presentation and in which there are so many unknown and uncertain factors Accordingly in collaboration with Professor Bradford Hill we have designed a strictly controlled clinical trial of anticoagulant therapy in this condition

Patients were considered who were under seventy years of age and had sustained a cerebrovascular accident at any time longer than fourteen days previously The patient attended the

hospital for one day during which a history was taken and a full clinical examination was carried out, along with investigations of cerebral cardiac and renal function The blood pressure was taken six times at hourly intervals with the patient lying supine

The usual contraindications to anticoagulant therapy were followed and in addition patients were excluded who for personal social or geographical reasons were unlikely to attend regularly for the necessary supervision The decision was taken as to whether or not the patient was suitable for admission to the trial by one doctor who did not know whether the patient would be in the treated or control group The patients admitted were separated by sex and thereafter randomised in pairs between the two groups one being known as the high dosage group and the other as the low dosage group Both received tablets containing phenindione (Dindevan) the former in an amount of 50 mg per tablet the latter 1 mg per tablet

The patients who did not know to which group they belonged were treated identically in every way attending one of four anticoagulant clinics staffed by three doctors The anticoagulant therapy itself was controlled by one doctor on the results of the prothrombin estimation The frequency of visits varied from weekly to four-weekly and at each visit blood was taken for estimation of the prothrombin time in both the high and low dosage groups

The aim in the high dosage group was to keep the prothrombin time as estimated by the Quick one-stage method between two and two and a half times the normal control The estimations were made by the same two technicians through the trial The amount of drug received by the patients in the low dosage group was insufficient to alter the normal prothrombin time

Many of the criteria for selection and details of control and management described above were based on the plan of the Medical Research Council trial of anticoagulant therapy in coronary thrombosis (M R C 1959) to which access was kindly granted and we gratefully acknowledge the help thus received

The first consideration in assessing the results of a trial of this kind is to see whether the system of randomisation has been effective in distributing the various factors which may influence the results evenly between the two groups Factors such as the age of the patient the site of their lesion the number of previous attacks and whether or not they were hypertensive were examined and in each instance it was found that there was no significant difference in the distribution of these factors between the two groups It can therefore be said with confidence that we have two groups of patients suffering

from cerebrovascular disease who are homogeneous with regard to relevant factors, and who have been managed in exactly the same way except for the fact that one group received effective anticoagulant therapy and the other did not

The trial began in October 1957 and was stopped in its present form in June 1959 because it had become apparent that the incidence of fatal cerebrovascular accidents due to cerebral haemorrhage was higher in the treated than in the control group It is apparent therefore that if one treats every type of cerebrovascular disease with anticoagulant therapy there is a liability to an increased incidence of death from cerebral haemorrhage This does not mean that anticoagulant therapy has no place in cerebrovascular disease for it may be that poor results in certain clinical sub-groups have overshadowed possible benefits to be obtained in other groups We have therefore amended the trial so as to exclude those who seem most likely to be at risk namely the hypertensive patients and we are continuing the trial in those groups for whom special claims have previously been made in the literature

✓[Meanwhile what is the general physician to do faced with a case of chronic cerebrovascular disease? It would seem to me that if he decides not to use anticoagulant therapy at all, he certainly is not in error On the other hand if he feels the need to undertake some form of therapy the strongest indications appear to be in patients without hypertension whose lesions are in the brain-stem and especially when they are experiencing recurrent cerebrovascular episodes <u>Recurrent episodes from a hemisphere lesion in normotensive patients might also be considered by some to be an indication</u> A more definite conclusion as to the role of anticoagulant therapy it is not possible to give at the present time]

I wish to express my thanks to the Trustees of the Nuffield Foundation whose generous support has made this work possible A full report is appearing in the Quarterly Journal of Medicine

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DISCUSSION

CHAIRMAN: I am sure you would wish m to thank Dr Mar hall for an excellent presentation of a very complicated problem which is very much in evidence at the present time We have had six papers on cerebro-vascular di ease which I am sure everyone would agree was a most appropriate subject to discuss in this College It is an interesting fact that a subject which has grown rather dull over the years hould have been so much resuscitated during the la t five or ten years until now it is a matter of very keen and general interest You will not have overlooked the fact that of the six papers which we have list ned to with such enjoyment two were given to us by urgeons and one by a radiologist I do not think that the association of the two points that I have made is accidental; I suggest that the thing which has done most to stimulate interest and inform knowledge on the subject of cerebro-vascular disease has been the advance of radiology and in its wake the enterprise of *surgeons who have felt that the results of radiology have enabled* them to attack problems which hitherto could not be attacked for lack of precise knowledge Now we have time for discussion and it is obvious that the subjects we have heard about fall into different groups I suggest that when the discussion begins we should try and bring together the points under each separate heading depending upon how they come up from the memb r of the conference The sort of headings we shall have will be matters of acute strokes from haemorrhage and matters ari ing from occlusive disease whether cerebral or intra-cerebral and I suspect questions will come up about anticoagulant th rapy

DR GARLAND: May I ask Profes or Rob before he operates on these carotid arteries what investigation does he make of the other arteries? I ask that because we have just had two disasters people with the stuttering onset of a left-sided occlusion and both with bruits over both carotid arteries and arteriograms showed that the left carotid was not supplying the right hemisphere but that the right carotid was supplying both It seemed therefore reasonable to operate on the left carotid and the operation was carried out *precisely as Professor Rob has shown* us Well of course a you know it is always very cold in Leeds but we did this under hypothermia as well and took every precaution but both these patients on recovering conscio isness had complete aphasia and right hemiplegia from which they have made only very partial recoveries

PROFESSOR ROB: We have not heard wh th r these vess ls were patent at the time of the operation or not which I think is important but I assume they were If I personally had seen a case with bi-lateral murmurs I would operate on both sides if I thought at the end of the first side that I had done a reasonable job and that it was going to stay patent Our exj erie ic is that it is probably wise if it i bilateral to do both at one sitting if possible

We only use anticoagulants locally into the distal arterial

tree during the operation In the early part of the series a number of th younger patients r ceived long term post-operative anticoagulants starting on the fourth day During the op ration we only use 50 milligram of heparin into th distal arterial tree locally

As regards what happ ns to the lining of the art ries - those two deaths were immediate deaths We hav had a number of later deaths and I would rather sp eak about what the artery looks like six months afterward than a we k aft rwards What appear to happen is that after you have taken the inside out of the artery it v ry quickly get covered by a layer f altered blood clot and this produces a mooth lining on the vess l The intima only grows a short distan e but nev r covers the whole defect unless the defect is very hort But certainly

a defect 2 centimetres long will never be cov red by the intima again In the gap b tw en you get a layer which looks like intima; if you look at it with the naked eye you cann t tell the difference It is only not intima when you put it to sev r tests a d it pp ars to be largely alt r d c llagen It i of interest and importan e that the thrombosis rate of thi vess l irre p tive of wh re it is is is low it is und r 10 per cent in our s ries of all thrombo ndarter ctomi s followed for quite a long time

DR COWEN: I would like to a k Dr Bull doe he get any false po itives fr angiograms? I understand that with some lesions something that looks like spa m I h itate to use the word occur and whether in fa t h get any false po itive that is to say indicating a lesion when there really i not one proved lat r? The oth r point i a minor one for Professor Rob but I would b v ry inter ted to know where xactly does he auscultat for th vertebral art ry?

DR BULL: I kno som times one an get false positives in the int rnal carotid art ry in the n ck but th y hav a slightly diff rent appearan e an gi graphically Had I m re time I would have hown one thi afternoon And they are of co r due to a p in tur which i not entirely sati factory and in which the contra t get under the intima and clos s th art ry in that ituation I think if one is experienc d one can spot th m I can r memb r that in thi case that I would have shown you whi h was a false positive we left the pati nt alone and r peated the angiograph a week lat r It wa th n perf ctly n rmal

Now with r gard to th intra- ranial ve sels uch as the anterior or middle cer bral I do not think one do s get a false positive and we alway ch ck th oc lusion on multiple pr j ctions a lateral an antero-posterior and an oblique at least In my opinion you do not g t false positives intra- r nially

PROFESSOR ROB: W have listened over the origin of the ver- t bral artery We think that th murmur is maximal at the area of th stenosis whichever ve sel is t nosed

DR BLOOM: I wond r wheth r I could get any help on the qu - tion of hypot nsive therapy in patient who have had erebral thr mbosis? The question I have always a k d wh n a pati nt i admitted with a v ry high blood pr sure who has had a troke i fir tly wh th r one should us anti-coagulant therapy and that has been answer d The next qu stion is wh ther one should bring down th blood pre sure particularly in patients who have a r ally high one I wonder wh ther we could be inform d on th t?

DR MARSHALL: I left it for som one who ha had a lot of xperience in hypotensive th rapy to say s m thing about this in the dis u ion b cau as I have tri d to indicate as far

as the cerebral side is concerned there is no satisfactory evidence as to what happens when you bring the blood pressure down in a large series of patients We all know that a further stroke can be precipitated but we do not know whether over all one gains or loses by doing this

CHAIRMAN: I wonder whether any members of the Conference who have a large experience of the use of hypotensive therapy would give the Conference the benefit of their experience of its effects in relation to the cerebral aspects of hypertension

DR PLUNKETT: I am concerned at a geriatric unit where quite a lot of anticoagulants are used I can remember one patient who was sensitive to the test dose and immediately got multiple thromboses and never picked up again That is the only one The ordinary run of very elderly hypertensives who stand the risk of going into failure have been treated with hypotensive drugs carefully but not lavishly We have not seen any strokes except just before they die of intercurrent disease or old age Then they usually go pale or funny for a day or so and one finds from the post mortem there are small multiple thromboses all over the brain which one would find anyway in such old people when they die

PROFESSOR McMICHAEL: I might try to say a little about experience in the use of hypotensive drugs in patients who have got cerebro-vascular disease As Dr Marshall said we all know that drastic r duction of the blood pressure in these people can in fact induce strokes in various varieties and this of course is a very grave drawback to the use of hypotensive agents in people with cerebral-vascular disease There are other interfering factors such as mental deterioration which make it quite impossible for them to follow a rather complicated regime and of course one must always remember the obvious which is not always remembered by general practitioners that once a patient has got a complete paralysis of one side there is nothing on earth that you are going to do with hypotensives that is going to restore his power It is in fact a very difficult situation and even when patients are being treated in hospital under our own eye they can occasionally develop a cerebral ischaemic episode For example one patient who had had his dose just after lunchtime went out of the ward and into a hot bath in the afternoon He th n stood up to dry himself and promptly collapsed with transient aphasia; fortunately he recover d So these patients are really in a very perilous situation and if hypotensive drugs are going to be used in them our general feeling is that we should not reduce the blood pressure too much Bring it down from say 240 systolic to 160-170 and try and be content with that, and also try to use hypotensive drugs which are reliable and fairly constant in their effects For example we had to use the early drugs such as pentolinium by injection to get a constant effect because of irregular absorption The new one, Darenthin has the same sort of drawbacks of irregular and incomplete absorption We had one or two pati nts on that one who have run into trouble so probably the best drugs to use are mecamylamine or the shorter acting pempidine in the treatment of this group But these patients who have definite evidence of cerebral vascular impairment really terrify me, and I do not like treating them at all if I can escape it

PRESIDENT: I agree with what McMichael has just said, with regard to our experience with hypotensive drugs but we have not done any controlled series Smirk in his series had come to the conclusion that the numb r of strokes in his follow-up cases was diminished since hypotensives had been used But at the same time he admitted when I last saw him that they had become more confident in the use of hypotensives and that

they were using them in milder cases in which they would not have used them in former years, so that they may have been treating a population in which you would not expect so many strokes at all However what I was really going to do was to ask Dr Bull a question if I may? Does he feel that there are any dangers in angiography specially after what on clinical grounds you diagnose as a thrombotic episode with brain stem symptoms?

DR BULL: I think th re are definite dangers in angiography I have not analysed completely Dr Marshall's theories from this point of view but I think we did have complications in about 10 per cent of cases Most of them if not all Dr Marshall will correct me were transient and in these cases we did attribute the regression to the angiogram, but fortunately it was usually shortlived I think that it is more dangerous to undertake angiography on patients with diseased arteries than for tumour or other le ions And what I would like to see is a modification of cerebral angiography in this type of case, and injection from some other site so that we fill the great vessels and do not traumatize them when we make the injection that is to say traumatize a vein elsewhere or an artery that is remote Then of course we will be able to see the mouths of the vertebral arteries too which is one of the points I tried to make earlier on this afternoon I would point out that one of the great difficulties in elderly people in catheterizing the femoral artery is that th iliac arteries are so frightfully tortuous that one cannot get a catheter up I think that is one of the problems we must get down to - sat sfactory cerebral angiography without traumatizing the vessels involved

SIR GEORGE PICKERING: May I ask a naughty question? This afternoon we have learnt what a lot of us have known for quite a long time and that is that we have to revise many of the views that we have long held about cerebral vascular disease I wonder if I could ask the question that really always both rs me How do you di tinguish between a ha morrhage and a thrombosis? I have always rather thought that headach practically did not occur in a thrombosis that loss of consciousness was less common and that of course patients with haemorrhage are much less likely to recover and they sometimes g t neck rigidity and they sometimes g t blood in the cerebro- pinal fluid But if you are going to operate on their brains - perhaps Mr McKissock might answer this - with what sort of confidence can you distinguish between haemorrhage and thrombosis?

CHAIRMAN: I know that Mr McKissock has views to express on the differ ntial diagnosis betwe n ha morrhage and thrombosis so I will ask him to speak on this question

MR McKISSOCK: I do not think you can tell wheth r a pati nt has got a thrombosis or a haemorrhage on clinical ground alone Headache can certainly occur with ha morrhage or with thrombosis Twenty to twenty-five p r cent of ca es of cerebral haemorrhage have no blood in the cer bro-spinal fluid either in the lumbar sac or in th ventricular system Two to five per cent of cases of cer bral ha morrhage have blood in the sub-arachnoid space at lumbar puncture or in the ventricular system These figures are ba ed on the two hundred and forty-four odd cases we have been talking about in hich quite a considerable proportion had no blood at ventricular puncture or lumbar puncture So I think all you can say and what I have said many times before is that you hould not mak on clinical grounds alone a diagnosis other than that of a ute cerebro-vascular accid nt and leave it as broad as that It then d p nds upon the oth r methods of inve - tigation lumbar puncture angiography po sibly ventriculography with air and in som ases ventriculography with myodil because you may have to press through all th e inv stigations b fore you

can tell exactly what is the matter And the best example I think of the need for this is in the cerebellar haemorrhages which I did not mention today but of which we have a series of over thirty now where neurological examination gives you no certain answer There may be blood in the subarachnoid space but again that does not give you a certain answer The carotid angiograms are negative the ventriculogram shows you normal lateral ventricles and a normal third ventricle and because the aqueduct and fourth are often so small you cannot get an adequate picture of them with air You then have to go to the length of putting myodil into the lateral ventricle in order to get a picture of the aqu duct and fourth ventricle and only on those pictures will you see the relatively slight shifts which indicate a haemorrhage into the pons the medulla or one cerebellar hemisphere So to reiterate I think the right diagnosis is acute cerebro-vascular accident which requires further investigation

DR FLETCHER: I am still a little perplexed about what cases should have these elaborate investigations I gather from Mr McKissock that the ones who are alert or at least drowsy are the only ones who do very much good on surgery and from Professor Rob that it is the ones who have not yet got any permanent changes who are worth having their arteries operated on Am I right here? And have we not got to do the full investigation on every acute stroke admitted in coma? If so are our resources up to this? It is rather important to know when you have to go ahead and do the full investigation and when you can sit back and be mercifully conservative

CHAIRMAN: I am certain we would all agree that Dr Fletcher has put his finger on an extremely important point Because from the administrative point of view and the management of patients particularly by those who are working away from the immediate vicinity of a centre where all these things are available - which are the patients to be chosen for this? If they are all sent clearly even British Railways would hardly be equal to the burd n Perhaps Mr McKissock you would speak to that one?

MR McKISSOCK: The first thing I think is that until several people have carried out controlled trials of urgical treatment versus medical treatment, in proven cases of haemorrhage or thrombosis whichever way you like to put it we do not know which patients should be subjected to this form of investigation On the other hand for the man who is out at the periphery unable to avail himself of all these things I would say that the patients he should send for this overall investigation are those who are alert or at worst drowsy but who nevertheless have fairly inten ive n urological signs from which it would seem unlikely that they are going to make a complete recovery In other words the pati nt who is alert or drowsy but with a total hemiplegia with or without dysphasia would seem to me to be an eminently suitable patient to send for this kind of investigation But remember this - that in those institutions hospitals where th se controlled trials are being undertaken if the material sent to th m is going to be selected in this way they ar n ver going to get the answer to their controlled trial This was brought very firmly to our notice over the controlled trial which we are carrying out on ruptured intracranial aneurysm which has been running since the beginning of January, 1958 One of our reasons for starting this trial was that we had looked through some 400 odd cases of ble ding into the subarachnoid space admitted to one department in a period of just over two years These 400 cases came from seventy to eighty hospitals and something like 110-120 physicians They were a very varied collection of clinical ca es as you can imagine but we took the trouble to send an investigator down to these seventy or eighty hospitals to go through all the case records of cerebro-

vascular accidents in those ho pitals for that period of two years during which time we had acquired 400 cases from them He found there 300 more cases Now th se hundred-odd physicians were selecting their cases They had sent a little more than fifty per cent to us for investigations Why? Was it because the patients were too old and sick to be sent or was it because they were so young that they did not wish them to be interfered with or thought they would recover anyway? We shall never know And so you are between the devil and the d ep sea in this If you want to find out you must take as big a cross-section of all cerebro-vascular accidents and investigate th m in this way in a controlled trial And if you are going to have a lot of selection at the periphery and only what are thought in the light of our present ignorance to be suitable cases for this form of investigation we shall get no further on

PROFESSOR ROB: I think that the stenosed carotid i the one where pur ly as a urg on one can get the best results On the other hand in the case of the thr mbosed carotid it is possibl that with improved techniqu and earlier cases one could get a good result in a number of them but that is a thing for the future W have not done it very often yet

DR MACQUAIDE: W have heard about hypot nsive treatment and anticoagulant treatment I would like advice on a very simpl point Those of us who live in the outback who have to make our diagnosis on clinical grounds how long are we to keep the e patients in bed? It se med to m that if it is a thrombosis early ambulation is not contra-indicated If it is a haemorrhage one ought to keep them rather longer

CHAIRMAN: I wonder who we could ask to answ r that question? Po sibly from the po t-operative cases - what is the practice in your unit Mr McKi sock?

MR McKISSOCK: In the cases of ha morrhage treated surgically we tart getting the patients out of bed if their physical condition p rmits of it that is if they are able to sit in a chair we would get them into a chair at forty-eight hours after evacuation of the haemorrhage And we would tr at them in an ambulant manner from that point on

DR MARSHALL: Yes I agree I tress the n ed to tr at things uniformly in a controlled trial Therefore w decided that as arly ambulation as possible should be the policy, and we have certainly s en no ill eff cts of this in thrombotic and we hav also had a seri s of ha morrhag s not so large in which we have se n no ill eff cts either

PRESIDENT: Could we know what the Chairman s views are n this subject?

CHAIRMAN: I entir ly agree I have n ver been convin d that putting a pati nt into bed did them any r al go d after a cerebral vas ular a cident and I think the sooner they get going the bett r

DR ----: I would like to ask Professor Rob please how pecific do s he consider the systolic murmur in the ne k to be? P rhaps I am bl s ed with an unusually perv rse crowd of pati nts but one doe hear systolic murmurs in th neck apart from the obvious condu t d murmur from the aortic valv such a the murmur in front of a prominent c rvical rib buttr and occasionally of course a rath r typical bruit from a large th yr i " re ar other aus for murmurs and I wonder wheth r we can be misled?

PROFESSOR ROB: It is important wh re the murmur is The c rvical rib murmur is in a different pla It is ven in a

different place from the vertebral artery murmur The carotid stenosis murmur is hardly conducted at all downwards It is simply a question of a murmur of maximum intensity at the site of an arterial stenosis The cervical rib murmur is quite easy to distinguish, and of course the thyroid murmur is entirely different

PROFESSOR McMICHAEL: Could I put one more question to Dr Marshall? Clarke and Murphy, who were working with me at one time on the problem of hypertension went into the cerebral manifestations in a number of patients One quite interesting small point that came out was that patients who got a cerebral haemorrhage very seldom or never gave a history of previous transient cerebral ischaemic episodes In the light of what we have seen about distal narrowing of arteries it may be that there is not enough pressure in the head to give those people cerebral haemorrhages and if so that might be a fairly useful small point in differential diagnosis I wonder whether this is borne out by Marshall s experience?

DR MARSHALL: I think Professor McMichael's statement is true, but however I would agree with Mr McKissock that the great bogey is our inability to distinguish, in a sufficiently high percentage of cases thrombosis from haemorrhage But I would also feel pessimistic that the presently available methods even taking the whole gamut of neuroradiological investigations, are not going to give us a sufficiently high percentage of success What we are in need of is an entirely different approach

DR WYMAN: May I ask one or two questions about hypertension in cerebro-vascular accidents? Have any of the previous speakers made any surveys showing any correlation between the incidence of hypertension and these accidents because I have seen a small series of figures which seemed to show that cerebro-vascular accidents were not really more common in hypertensives than in normotensives Another question, Mr McKissock mentioned one form of cerebral haemorrhage which was more prevalent in hypertensives I would like to know whether the diagnosis of hypertension was based on previous knowledge of the patient or merely on the readings of the blood pressure taken after the cerebro-vascular accident had occurred which of course I should imagine would be very unreliable

CHAIRMAN: May I call upon you again Dr Marshall for that question of how far one can establish that hypertension, when present has been present for a long time?

DR. MARSHALL: I can only answer the second question, not the first because I have not had enough experience of hypertensives But as regards the second a blood pressure taken after the accident has occurred is totally unreliable We have had several people in our long-term trials attending every week with a record of their blood pressure and they have had an accident and we have seen what the blood pressure does It can fluctuate wildly during the first forty-eight hours and I think blood pressure so taken will have very little relation to the blood pressure recorded before The only way you can tell whether they were hypertensive before is by the examination of the retina size of the heart and that sort of thing

DR CAMERON: It is very difficult sometimes to have enough surgical accommodation and Mr McKissock made plain the position If you can only admit a certain number into a unit for each month then you have to choose who are the ones who you think will derive the most benefit The next point I wanted to ask is whether anyone has tried anything on the lines of what some years ago we tried? A young patient came in with sub-arachnoid haemorrhage We were fairly confident it was a haemorrhage because there was blood in the cerebro-spinal fluid Now we gave the patient anti-

hypertensive treatment intravenously and tried to get the blood pressure down and at the same time drained the cerebro-spinal fluid Indeed it seemed to u at the time that the coma was lightened and that the case was more likely to recover

MR McKISSOCK: I have no xperience of this at all I am sorry

DR CADMAN: Two questions I would like to pose the first one probably to Dr Hutchinson I have recently had a case of the Millard-Gubler syndrome that is a sixth nerve paralysis and a seventh nerve paralysis on one side and a hemipl gia on the opposite side Is it possible to be more sp cific about the actual artery involved or must one say that it is the basilar art ry? The s cond qu stion is one direct d to Professor Rob I think it is possible to feel through the back of the mouth inside the internal carotid artery Is this a physical sign of any value in th diagnosis of thrombosis of the internal carotid artery or stenosis?

DR SHAW: As regards the differentiation between basilar yndrome and any other type or indeed the vertebral as well I do not really feel that it is any easier to do than it is in the forebrain

PROFESSOR ROB: Unfortunately I feel that I cannot tell the difference betwe n a patent and an occluded internal carotid artery The reason is that it seems to get moved up when it is clotted by the pulse in the common carotid below

CORONARY ARTERY DISEASE

Chairman—D Evan Bedford

Epidemiology and Diet

J N MORRIS

I will say something about the dimensions of the problem and on pathogenesis then a little about aetiology and the present status of the dietary hypothesis

I

Table I gives some rough estimates from various surveys of the current prevalence in Great Britain of coronary disease

TABLE I

PREVALENCE OF CORONARY DISEASE

MEN AGED 60-65

		Rough Estimates
I	Coronary atheroma	c 100%
	Much coronary atheroma	20-33%
II	Coronary occlusion	10-20%
	Multiple occlusion	
III	Clinical cor heart disease	3-15%

Various surveys Great Britain 1950 s

clinical and pathological However inaccurate the individual figures may be the table probably gives useful orders of magnitude Thus "imagining" men in their early 60's there are unlikely to be any sizeable social groups with a lower prevalence than 20% of extensive plaque formation in the walls of the coronary arteries and the range may well be no more than 20-33% The next figure to look at is the last the implication is that the majority of middle-aged men having much coronary atheroma do not suffer from clinical coronary heart disease The fraction would probably still be a minority if the figure of 3-15% were increased to include also sub-clinical coronary heart disease with ischaemic myocardial fibrosis or significant electrocardiographic abnormality alone

Intervening of course between disease of the walls of the coronary arteries (coronary atheroma) and coronary heart

disease is coronary occlusion and with increasing occlusion there is increasing incidence of heart disease (In "occlusion is included frank acute thrombosis and complete or near-complete chronic obliteration usually fibrous and the product of organised thrombosis) When there is an increase of mural atheroma lumen occlusion is more likely to develop but coronary occlusion is not the same as nor any simple function of coronary atheroma The answer to the question whether there are in fact two processes or two diseases in coronary "atherosclerosis" is in epidemiological terms yes The historical material (Table II) suggests that during the present century there has been an increase of coronary occlusion but there is no evidence that mural atheroma has increased and, indeed it was rife before the First World War The evidence is that not only has such occlusion increased but acute thrombosis also and cardiac infarction ruptured ventricle ischaemic myocardial fibrosis The same kind of dissociation between mural and lumenal disease is becoming evident in geographical pathology as in Jamaica where it seems that coronary atheroma, but not occlusion is highly prevalent Further when men dying from some disease other than coronary heart disease are classified at post mortem by occupation there are little if any differences in the amount of coronary atheroma in the various groups (Table II) but coronary occlusion is almost twice as common in light workers as in heavy Finally as said when there is more mural atheroma occlusion is more likely to supervene, and this is illustrated in hypertension it is possible however for occlusion to increase when there is no increase of the atheroma as we have seen in deaths from peptic ulcer

Various prospective studies have found that presumably healthy men who have high blood lipids or high blood pressure - it is usually essential hypertension - are specially liable to develop clinical coronary occlusion and coronary heart disease Hypertension almost certainly and raised blood lipids very likely are causes of coronary atheroma Whether they are direct causes also of occlusion and heart disease is not yet clear The Framingham study and our own of London busmen have now shown that blood pressure and blood cholesterol levels are independent of each other Men with high blood pressure are not particularly likely to have high blood cholesterol etc - there seem to be two distinct disorders However high blood pressure and high blood cholesterol are very common and they do coincide in individuals When this happens the outlook is serious in the Framingham study about a quarter of the men with blood cholesterol over 300 mg % and diastolic pressure over 115 mm Hg developed coronary heart disease within six

TABLE II

CORONARY "ATHEROSCLEROSIS"

A RECENT TRENDS

Prevalence in Deaths from Injuries Infections Cancer
Men Aged 45-60

Coronary Atherosclerosis	1908-13[1] (530) %	1954-56[2] (1394) %
Mod and much mural atheroma	53 0	34 0
Severe narrowing and lumen occlusion	1 3	4 9
Calcification present	19 0	10 0

1 London Hospital
2 National Necropsy Survey

B IN OCCUPATION GROUPS[1]

Prevalence in Deaths from some other cause than
Coronary Heart Disease[2]
Men Aged 45-70 incl

Coronary Atherosclerosis	Occupation		
	Light (1392) %	Active (1377) %	Heavy (836) %
Much mural atheroma	21 0	17 0	18 0
Lumen occlusion	5 9	4 0	3 1
Calcification present	23 0	20 0	21 0

1 National Necropsy Survey
2 Excluding only the small number of cases with secondary (mostly renal) hypertension
(Numbers of cases in brackets)

years Clearly the discovery of such levels in presumably healthy men is a clinical emergency and controlled trials are urgently wanted of the methods available for helping them This

is an illustration of one of the main uses of epidemiology to clinical medicine the identification of "susceptibles", of a vulnerable group of individuals (Obesity may be a third easily recognisable precursor though how independent of these two remains to be settled)

Questions arise about the norms of blood lipids in the population A current survey of London busmen shows that drivers and conductors have different levels After 50 or 55 years of age differences in average blood cholesterol are almost as large e g 16 mg % as is commonly reported when cases of coronary heart disease are compared with "controls" (at younger ages the contrast between cases and controls is of course more pronounced) In general little is known of the distribution of blood lipids among groups in this country What is physiological and what optimal? The interim answer from two epidemiological studies Framingham and Albany seems to be that coronary heart disease is uncommon among men whose serum cholesterol is less than 200 mg % It is likely, however that most middle-aged males in Western countries have higher values Measurement of β-lipoprotein and of plasma triglyceride may prove to be finer predictors because closer to the metabolic disturbances involved As to blood pressure it has been uncommon in Framingham for middle-aged men with diastolic readings consistently below 85 to develop the disease In Framingham such men were a small minority

II

The first point to make about aetiology is that no method is yet known of reproducing coronary heart disease with any certainty in the experimental animal (though there are at least two promising approaches) I mean a method that will induce coronary atheroma and then, erosion of a plaque thrombus formation with occlusion, myocardial infarction Even if there were such a method it would be quite essential as in all chronic diseases to test the findings in actual human experience

In terms of diet, today's principal hypothesis on cause the only thing approaching a hard fact is that under-nourished populations eating little animal fat suffer little coronary heart disease It is not merely a question of poverty because Japanese who eat little animal fat for historical and cultural reasons rather than simple poverty also appear to suffer little from coronary heart disease Nor is the immunity racial since Japanese men migrating to the U S A seem soon to develop "western" rates of coronary heart disease and this may be true also of the largest Japanese cities Interpretation of these findings is not easy People of under-developed countries

differ in so many respects from those of developed (or over-developed") countries - e g in other aspects of the diet in mental outlook in physical activity - that the investigator is soon trapped in the maze of the Western way of life" and Western material standards from which he has been unable to escape Moreover the past medical history of middle-aged individuals in under-developed countries is so different from that in the West that no sensible "standardisation" for comparison is possible There is little evidence yet of any gradation of heart disease with increasing "westernisation" - there are few observations except on the extremes

Among the advanced Western countries themselves there are substantial differences U S A for example registers about three times the death rate of Sweden - both are in the highest "mass consumption" stage with very high total fat and animal fat consumption Finland and Austria or Canada and Norway provide other contradictions Several years ago Keys tried to associate national death rates from coronary or arteriosclerotic and degenerative heart disease with total fat consumption of countries but interest was lost because of the inadequacies of the data on both sides of the equation certified mortality from particular causes can be compared with confidence among few countries and the ground is even less firm when crude national food statistics are used as indicators of what people eat Recently there has been a revival in this approach as claims have been made of a striking correlation between national death rates and the consumption of saturated fats From experimental work it will of course be expected that the association between the type of fat blood lipids and heart disease is far closer than that with total amount of fat Table III summarises the main findings and the last column is obviously far more interesting than the preceding two But I am at a loss to understand the figures Thus the very high Norwegian figure of 21% of calories from polyunsaturated fat seems to assume that very large quantities of whale oil are consumed neat and unsaturated However whale oil is inedible as such and in the process of hydrogenation to produce margarine fatty acids are "saturated" in some or considerable measure In general the high figures of polyunsaturated fats are all for countries making their returns to the Food and Agriculture Organisation in the form of constituent oils e g whale oil and the low figures are from countries reporting foods e g margarine

The answer to these questions about international differences in coronary heart disease in relation to the mode of life can only come from appropriate field surveys Keys has pioneered these W H O is trying to promote them and I fancy that if

TABLE III

MORTALITY FROM HEART DISEASE AND FAT CONSUMPTION

Country	Mortality[1]	Total Calories[2]	% Calories from Fat		
			Total[2]	Animal[2]	Polyunsaturated[3]
U S A	449	3070	39	27	5 7
FINLAND	394	3170	31	25	2 7
CANADA	372	3130	38	29	3 0
AUSTRALIA	344	3160	38	32	3 2
NEW ZEALAND	306	3370	40	36	2 2
UNITED KINGDOM	249[4]	3270	38	26	3 4
W GERMANY	179	2950	36	23	12 6
BELGIUM LUX	176	2980	35	24	10 6
DENMARK	170	3370	38	28	12 8
SWITZERLAND	156	3100	34	23	10 0
NORWAY	154	3130	38	29	21 0
AUSTRIA	151	2820	31	25	7 4
SWEDEN	147	3070	39	30	11 1

1 Mortality per 100 000 from Arteriosclerotic and Degenerative Heart Disease B 26 in Men Aged 50-55 W H O

2 Food and Agricultural Organisation

3 From Jolliffe

4 *England and Wales*

All figures about 1954/55

there is another Conference like this in five years time the report of such studies will replace the present fragmentary and unsatisfactory information

Blood Lipids

There is much evidence relating these to diet on the one hand and to coronary heart disease as already mentioned on the other The control of blood lipids is now a very active field of inquiry stimulated by the discovery of the power of *saturated fatty acids to raise* blood *cholesterol levels and of* polyunsaturated to lower them However, there are few studies attempting to relate diet blood lipids and heart disease all three together Ecological studies do, at the extremes Thus the under-nourished populations suffering little as already stated from coronary heart disease have low blood cholesterol levels In Cape Town the three variables were associated among three racial groups at different stages of social-economic

development Samples of Japanese men in Japan Hawaii and California have increasing blood lipids and there is increasing coronary heart disease among them in that order associated with changes in diet Western countries as a class have high levels and much coronary heart disease Within these countries illustrated in Table III no correlation is yet evident between the vital statistics and what little is known of prevalent serum chol sterol levels More serious there are no prospective studies in the West (or anywhere) of individuals their food habits blood lipids and personal experience of coronary heart disease other variables now thought important being held constant And there is very little of retrospective study either The emphasis in all I am saying is on lack of evidence and not on negative results Surprising though it may sound little work is at present being done on many of these questions They are of course frightfully difficult

The chief obstacle to the prospective survey of large numbers of individuals is the lack of a simple method of describing individual diet Various research groups are now tackling this question My colleagues and I are seeking simple indicators that correlate highly with the week s individual weighed diet which is the best measure outside the metabolic ward of what an individual actually eats Usable indices are being produced thus among the bank staff studied the number of slices of bread + the number of times visible milk is drunk correlate at 0 66 with total weighed fat consumption However such little reconnaissance as we have attempted of the next step gives us little encouragement to proceed with large-scale investigations for no association whatever is evident so far between our measures of fat intake by weighing and the individual blood cholesterol or β-lipoprotein level Studies in the U S A using different methods are also beginning to produce the same result This reminds us of another aspect of the problem There is little if any evidence that minor manipulations of the diet such as are now so commonly practised in the U S A will effectively lower blood cholesterol and keep it low though drastic changes in the diet e g a reduction in total fat and the substitution of two thirds of the animal fat by corn oil will assuredly do so *

* There is little if any evidence that such lowering will reduce the subsequent occurrence of coronary heart disease though this may be another story Again necessary facts understandably are scanty

What little we know or dare surmise about the relationships of "Western" death rates from coronary heart disease to national food consumption on the one hand and about dietary experiments with blood lipid levels on the other does raise the question whether the association between diet and coronary heart disease is linear i e whether there is a proportionate dose response" of heart disease throughout the range of food intake It may be that all Western countries and nearly all Western individuals are above the threshold or safety level of diet - but that a wide range of coronary experience is nevertheless still possible even in the constitutionally prone It is urgent to clarify this issue

Very relevant is the growing incidence that other aspects of diet as well as the fatty acid composition affect blood lipid levels and that non-dietary factors also do so The most interesting work recently has been on the latter and it is evident that physical activity smoking and stress' are influential At present all these seem to be marginal or "super"-normal factors affecting blood cholesterol levels above the 200 mg mark though few studies have attempted to isolate each at various dietary levels and estimate their additive effect Moreover there are other mechanisms or pathways to coronary heart disease than high blood lipids (essential hypertension has already been mentioned) and luxus-sophisticated diet physical inactivity cigarette smoking and the modern social-psychological environment may also be involved in these Thus we are back again in the maze of the Western way of life" and maybe this represents the truth - that indeed coronary heart disease is multifactorial with many causes acting and reacting on each other to disorder cardiovascular functions and produce the disease If it is so the position becomes more hopeful There may be more than one way out of the maze, more than one way of reducing coronary heart disease

I am grateful to my colleagues in the Social Medicine Research Unit for much help

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Sex Differences

M F OLIVER

Clinical Studies

The clinical features of coronary heart disease occur more commonly in men than in women This male predominance was first suggested by Heberden (1802) and has since been confirmed In Britain, the male/female ratio for coronary heart disease has been variously assessed at 7/1 (Mackenzie 1923) at 4/1 (Cassidy 1946 Peel 1955) 3 3/1 (Oliver and Boyd 1955) and 2 4/1 (Ryle and Russell 1949) This sex ratio decreases with advancing age For example the male/female ratio of 1 000 consecutive patients admitted to the Edinburgh Royal Infirmary for treatment of angina or of myocardial infarction (all had confirmatory electrocardiographic changes) decreased from 16/1 under the age of 40 to 7/1 between 40 and 49 to 5/1 between 50 and 59 to 2/1 between 60 and 69 years and 1/1 over 70 years Although coronary heart disease occurs infrequently in women in their thirties and early forties 63 women under the age of 45 years have attended this Department during the last 6 years with clinical features of coronary heart disease In 52 of these (Table I) there was electrocardiographic

Table I

Health of Coronary Patients	Numbers
Healthy (2 were pregnant)	9
Premature menopause	19
Hypertension (DBP > 110) (2 were also pregnant)	18
Xanthomatosis or hypercholesterolaemia	6
Diabetes mellitus	3
Anaemia (Hb < 55%)	3
Aortic valve disease	3
Cushing s disease	2
Myxoedema	2

The health of 52 women who developed coronary heart disease under the age of 45 more than one disorder was present in several women

evidence of myocardial ischaemia or infarction In 37 per cent menstruation had ceased before the onset of their first symptoms this was due either to surgical removal or radiation of the ovaries or to a spontaneous premature menopause and this observation confirms and amplifies the findings of Spitzer et al (1957) Severe hypertension was present in nearly one third and coexisted with other disorders in some endocrine diseases were also common This analysis indicates that a premature menopause is at least as important as severe hypertension in the development of features of coronary heart disease in young women

The decrease in the male/female ratio with age is due partly to a disproportionate increase with advancing years in the incidence of coronary heart disease in women It is of course well known that the peak incidence of coronary heart disease occurs in women between 60 and 65 years and is five or ten years after the peak incidence in men (Hedley 1939 Master et al 1939 Peel 1955) but the rapidity of the increase in the incidence of coronary heart disease in middle-aged women is less generally recognised Although there are more male deaths from coronary heart disease at all ages a recent analysis of the Registrar-General s statistics has indicated that between 40 and 69 years the rate of increase in coronary heart disease in women is three times that in men (Oliver and Boyd 1959) This observation suggests that the involutionary changes of the menopause are directly associated with the development of coronary heart disease in some women and this is supported by the finding that women who have had both ovaries removed before the age of 35 developed coronary heart disease prematurely and more frequently than a comparable control group of women from whom only one ovary was removed (Oliver and Boyd 1959)

These sex differences in the incidence of coronary heart disease are apparently less marked in primitive communities (Walker et al 1956) and in the American negro population (Weiss and Gray 1954)

Pathological Studies

Autopsy studies also indicate that coronary atheroma occurs more commonly and to a greater extent in men than in women but the differences between the sexes is less marked than it is for the clinical manifestations of the disease Indeed Lober (1953) estimated that under the age of 40 the male/female ratio for atheromatous lesions of the coronary arteries was no more than 4/3 Holman et al (1958) studied the incidence of fatty streaks in the aorta of white and negro populations in the United States and reported a definite male predominance in the whites under the age of 40 but in contrast there was

a female predominance in the negroes An autopsy study of the incidence of myocardial infarction has also indicated that under the age of 50 there is in the white population a male/female ratio of about 4/1 yet no such sex differential exists in a negro population study under similar circumstances (Thomas et al 1957) This lack of any significant sex difference in the negro both in the incidence of clinical coronary heart disease and in the autopsy assessment of coronary atheroma and of myocardial infarction has not yet been adequately explained Further support for the view that sex influences the incidence and degree of coronary atheroma can be obtained from the observation of Wuest et al (1953) and Rivin and Dimitroff (1954) who report more coronary atheroma than normal in women from whom both ovaries had been removed similarly Hawke (1950) observed less coronary atheroma in eunuchs when compared with normal men

These clinical and pathological studies suggest that sex differences in the incidence of coronary heart disease are largely determined by physiological changes in ovarian function

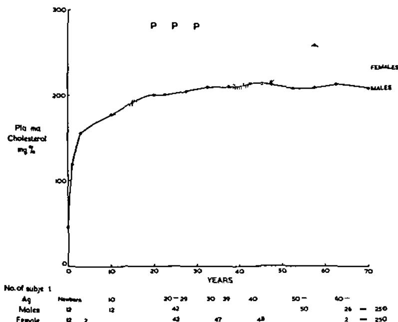
SEX DIFFERENCES IN THE PLASMA LIPID LEVELS

It is well established that the plasma lipids are often abnormal in patients with coronary heart disease and the sex differences in plasma lipid levels correspond closely to the sex differences in the incidence of coronary heart disease

In Health

In health plasma lipids and lipoproteins alter according to age and sex In Figure 1 the influence of age and sex on the plasma cholesterol level is shown semidiagramatically for this purpose the changes which occur in the concentration of plasma cholesterol can be regarded as representative of alterations which occur in beta-lipoprotein cholesterol These analyses have all been obtained from healthy members of the University and hospital teaching clerical technical and domestic staffs, and also from students and from patients receiving physiotherapy following a fracture From this figure certain features emerge The plasma cholesterol of newborn infants of both sexes is low but rises rapidly after birth (Sperry 1936) In males, the plasma cholesterol gradually rises up until the middle thirties and thereafter, in Britain it remains more or less constant these findings agree well with those of Adlersberg (1956) In females the plasma cholesterol level fluctuates over a wider range and has three main influences - the menstrual cycle the menopause and pregnancy

With each menstrual cycle, the plasma cholesterol and beta-



Figu 1 The influ nce of age and sex on the plasma chole t ol l vel n h alth

lipoprotein cholesterol varies regularly and at ovulation they are significantly lower than at any other time in the cycle the plasma cholesterol may be as much as 20 per cent lower than the level during the preceding and succeeding weeks (Oliver and Boyd 1953a 1955b) Following the menopause the plasma cholesterol rises abruptly and in women in the 50-59 age quinquennium it is about 35 per cent higher than in women twenty years younger (Oliver and Boyd 1953b 1959) Since the plasma cholesterol and beta-lipoprotein cholesterol rises after the premature surgical removal of both ovaries (Robinson et al 1957 Oliver and Boyd 1959) the post-menopausal elevation of these lipids is probably due at least in part to ovarian involution and withdrawal of endogenous oestrogen secretion That endogenous oestrogen secretion may be closely related to plasma lipid fluctuations in healthy women is further emphasised by the fact that oestrogen secretion is maximal at ovulation (Smith and Smith 1936 Brown 1955) which is the phase in the menstrual cycle when the plasma cholesterol is lowest Moreover administered oestrogens lower the plasma cholesterol and beta-lipoprotein cholesterol (Eilert 1949 Barr et al 1952 Oliver and Boyd 1954 1956) In pregnancy

(represented in Figure 1 by the letters P) the plasma cholesterol rises during the last three months by about 50 per cent and does not approach the normal non-pregnant level until three or four months after confinement The hypercholesterolaemia of pregnancy has not yet been explained (Oliver and Boyd 1955) and is the opposite of the expected in terms of endogenous oestrogen secretion

The plasma lipid and lipoprotein pattern in advanced pregnancy is similar to that seen in patients with coronary heart disease and one question which arises is whether the arterial intima is harmed by such episodes of hypercholesterolaemia Various authors have reported the presence of many fatty streaks on the aortic intima in advanced pregnancy and in order to investigate this problem further two surveys of the relationship of parity to coronary heart disease have been undertaken in women over the age of 45 years In the first survey, the parity of 500 women admitted consecutively with electrocardiographic evidence of myocardial infarction was contrasted with the parity of 500 relatively healthy women who attended hospital for treatment of superficial injuries burns minor fractures or appendicitis In the coronary heart disease group there were fewer unmarried women (Table II) and more with large families

Table II

	Age in years	Total Number	Unmarried women	Percent of unmarried women
Coronary disease group	63	500	61*	12 2
Hospital control group	63	500	109*	21 8
Census (1951) control group	60-64	33 554	7 063	21 0

A survey of marital status in women with coronary disease women with superficial injuries burns minor fractures or appendicitis and healthy women in the south-east of Scotland

* $P < 0\ 01$

(Table III) In the second survey the parity and incidence of coronary heart disease was determined for all women over 45 in a general practice and all women over 45 who attended a Casualty Department for treatment of superficial injuries burns or

Table III

CORONARY PATIENTS OVER 45 YEARS

	Total Number	Number with 4 or more pregnancies	
Hospital Controls	439	135	
Coronary group	439	170	0 02 > P > 0 01

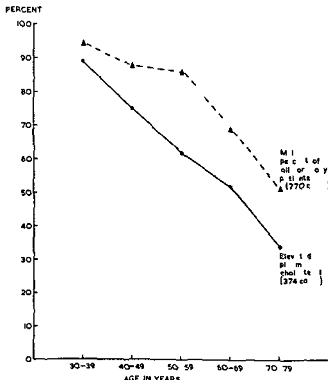
HEALTHY WOMEN OVER 45 YEARS

	Total Number	Number with coronary disease	
3 pregnancies or less	450	18	
4 pregnancies or more	316	23	0 10 > P > 0 05

minor fractures over a period of six months (Table III) Although less significant than the first survey this also suggests that coronary heart disease may be more prevalent in women with large families similar observations have been made by Winkelstein et al (1958) These preliminary results are far from conclusive They are obviously open to many interpretations and do not necessarily indicate that repeated exposure to the hypercholesterolaemia of pregnancy is harmful to the arterial intima There must be many variables for example hypertension and obesity are more common in multiparous women and the stress of caring for a large family must surely be considerable

In Coronary Heart Disease

The chief sex difference in the plasma lipids of patients with overt coronary heart disease is that hypercholesterolaemia is more often present in young men than in young women indeed normal plasma lipid levels are uncommon in young men with coronary heart disease (Oliver 1958) How much this is an expression of masculinity is difficult to assess but it is known that androgens elevate the plasma cholesterol and beta-lipoprotein cholesterol (Barr 1953 Oliver and Boyd 1956) In contrast hypercholesterolaemia is not particularly common in young middle-aged women with coronary heart disease and in this group hypertension occurs more commonly In Figures 2 and 3 these sex differences in coronary heart disease and the incidence of hypercholesterolaemia are illustrated The figures for the incidence of coronary heart disease have been derived

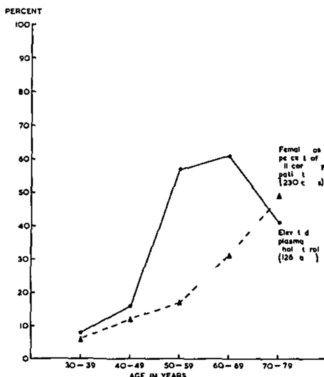


F gure 2 The age distribut on of consecutive male pat ents w th acute myocardial infarction or i chaemia and the incidence of elevated se um cholesterol level as estimated three o more months lat

from the 1 000 consecutive patients with myocardial infarction or ischaemia to whom reference has already been made and the figures for elevated plasma cholesterol levels were derived from plasma estimations made in 500 of these patients three or more months after their recovery from the acute episode The arbitrary choice of a particular figure to act as the dividing line between elevated and normal plasma cholesterol levels has already been described (Oliver 1958) In Figure 2, the male predominance in the incidence of coronary heart disease under the age of 50 and the frequency with which elevated plasma levels occur in these young men are both shown In Figure 3 the post-menopausal rise in the incidence of coronary heart disease and in plasma cholesterol are both illustrated

SUMMARY

Clinical and pathological studies of sex differences in the incidence of coronary heart disease suggest that they are



Figu 3 Th age d stribut on of consecut ve female pat nts with acute myoca d al infa ction or ischaemia and th inc d nce of elevated rum choleste ol levels as e timat d three o mo e month lat r

derived partly from physiological changes in ovarian function

With the exception of pregnancy sex differences in the plasma lipids in health are probably due largely to physiological changes in endogenous oestrogen secretion

In both sexes the incidence of coronary heart disease and the incidence of elevated serum lipid levels are positively correlated

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Radiology

A G LEATHAM

I shall remind you of a technique for coronary angiography in live dogs which has been developed in the Cardiac Department of St George s Hospital by Drs Graeme Sloman and Keith Jefferson (1960) and was presented at the last Meeting of the Association of Physicians I will then describe improvements wh ch have been recently carried out by Dr George Michell and Mr J Davies I apologise for discussing a technique to a body of clinicians but the development of a safe method for performing coronary angiography is of vital importance in the development of our knowledge of coronary disease and of its treatment It should prove of value in

1 The differential diagnosis of pain in the chest
2 Studying the natural history of coronary disease
3 Assessing the results of medical and surgical treatment
4 As a pre-operative test to study the localization of the disease if a suitable operation should be devised

To obtain satisfactory visualisation of the coronary arteries the contrast medium must be injected into a coronary artery or into the ascending aorta, and this is usually made through a catheter which has been inserted into the right brachial artery Dr Mason Sones of Cleveland has perfected the coronary artery injection technique but it is felt that the injection of one vessel at a time may result in differential anoxia of the myocardium and the risk of ventricular fibrillation Our injection of 0 8 - 1 cc of 85% Hypaque per kg of body weight has been made into the ascending aorta just above the aortic valve through a catheter with spirally placed side holes and a blocked end hole To obtain good visualisation Sloman found like others before him that it was necessary to induce sinus bradycardia or cardiac arrest with acetylcholine (Dotter and Frische 1958) (Figure 1) Acetylcholine proved safe in over 100 experiments in this department and has been used in human subjects in France (Arnulf and Chacornac 1958) but potentially it is expected to be a dangerous procedure and we have sought a safer method

Gregg (1950) has shown that coronary flow is almost confined

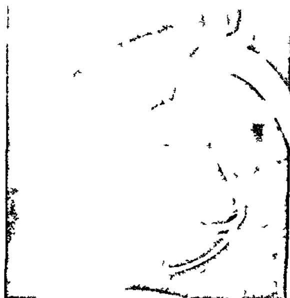
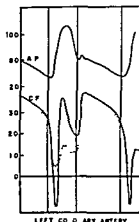


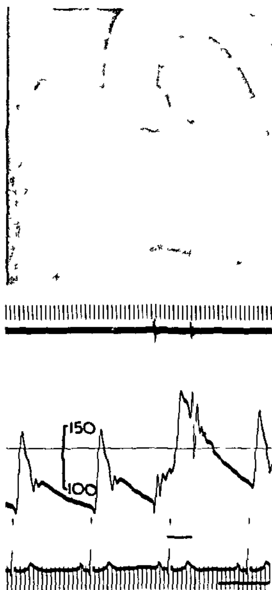
Figure 1 Coronary angiogram in a dog Injection made during acetyl choline arrest

to diastole (Figure 2) and injection of contrast medium in diastole avoiding systolic dilution was suggested by Richards and Thal (1958) Mr J Davies in our Department has developed an electronic device using relays fired by the QRS of the electrocardiogram which actuate a Talley injector (Pattinson and Somerville 1958) after an interval which can be varied to

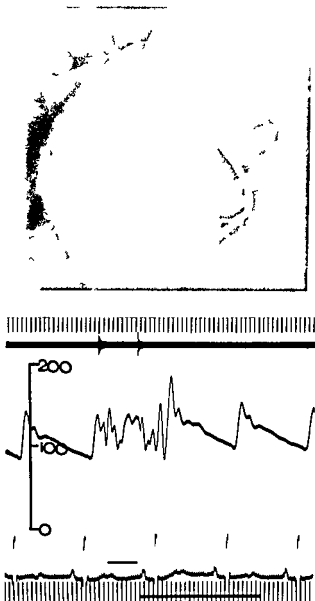


Figu e 2 Gregg s diagram showing dominance of coronary flow in diastole A P is the aortic pressure CF is coronary flow

suit the *individual heart cycle* The *difference* between systolic and diastolic injection is illustrated in Figures 3 and 4



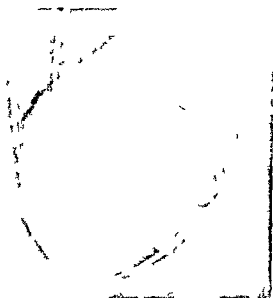
F gure 3 Co onary ang og am w th nj ct on mad du ng yetole The eco d ng shows th t m ng of th inj ct on in elat on to the el ct o a d og am & o tic p e sure pul e The top trac ng wa p oduced by the sound of the nject on the line d awn hor zontally above the E C G show the actual tim ng of the njection into th aorta aft co ction fo lag Th beginning of the line b low th E C G s an autom tic ind cation of th moment of x ray exposu e The co ona y a t • poo ly hown a xpected



Figu 4 Co onary angiogram with injection made during diastole and consequently better filling of coronary arteries Th film was taken in the same diastol as the inj ction to how proximal coronary filling

The x-ray techniques are of vital importance in obtaining good coronary angiograms Using an indirect technique with a Philips amplifier and cine camera at 32 or more frames per second transient filling of coronary arteries is not missed and it may be possible to detect retrograde flow beyond an obstructed vessel

We have also employed direct radiography for this will always yield greater detail Using a Schönander cassette changer with six films a second it was found that exposures made immediately after the injection in the first diastole showed the best filling of the proximal coronary arteries (Figure 4) while exposures made in the second diastole were best for the distal branches (Figure 5) Since the use of a single film yields an even clearer



Figu e 5 Coronary ang og am w th njection m d in d a tole and film taken n th e ond d a tole to show filling of d stal b an h s

picture and avoids the need for an expensive film changer the automatic injector has been arranged to give two (or more) injections in succeeding diastoles This technique has produced very good filling of both proximal and distal coronary arteries in one film (Figure 6)

Our conclusion is that the coronary arteries of live dogs can be adequately consistently and safely filled with contrast medium by the use of special techniques and that it is now justifiable to apply the procedure to human subjects



Figure 6 Coronary angiogram using a single film following two diastolic injections There is adequate filling of both proximal and distal b anches

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DISCUSSION

CHAIRMAN: I am sure you have some points you would like to raise or questions you would like to put We as practi ing physicians, are concerned with these tatistical and epid miolo-gical studies indirectly, that is to say we want to know wh ther as yet we are justified in altering the dietary habits or hab-its in regard to work and exercise, of our patients or whether we are justified in giving to mal patients oestrogens and so forth So I will ask anyone who wishes to speak to do so now

DR FLETCHER: Could I ask Dr Oliver a simple question? The male/female ratio of his young patients in hospital was nineteen to one and mortality ratio four to one? Now does this mean that there is a diff rential diagno tic error coming in h re or is coronary disease any more fatal a dis a e in young women than in young men to raise the relative mortality compared with admission figures?

DR OLIVER: The male/female ratio is certainly in a very small group i e 19 to 1 in the under 35 group I think that we should not pay too much attention to this because there was only one woman in that particular analysis Could we put it more at th level of 10 to 1 not 19 to 1 Becaus und r forty-five if you put together all the m n and women you get about 10 to 1 which i a more r asonable figur We hav no evid n that ther is a differ ntial male ratio in mortality

DR McDONALD: I would like to ask Dr Oliver whether in the patients who developed cardiac infarction while still menstrua-ting there was any evid nce of a peak incidence at any phas of the menstrual cycle or whether the dates of infarction were v nly spread throughout the cycle

DR OLIVER: I am afraid that I cannot answer that I cannot tell you the r lation of the menstrual cycle and th pattern of cardiac infarction

DR WILLIAMS: May I ask Dr Oliver if he has any infor-mation ab ut thyroid function and its cyclical changes during m nstruation and its relationship to serum-cholesterol in wom n

DR OLIVER: I have no information about that Sir I am aware that there i a cyclical change it does not fit in with the change in cholest rol I understand that the alteration in protein-bound iodine(PBI 131)that does occur during the menstrual cycle is not that which on would expect in relation to th change in cholest rol Indeed it is low r immediat ly before m nstruation than at ovulation

DR KEMBALL PRICE: Morris did mention the subject of nervous stre s He passed it over rath r quickly As a clinician one is impre ed by the number of tim s one ees myocardial infarc-tion pre ipitated by exceptional nervou strain and one reali that it is a very difficult matter to as ess statistically I

wonder whether any work is being done to investigate that aspect?

DR JACOBS: I would like to ask Dr Morris whether he has any data on (i) relation of coronary disease to body type and (ii) of blood lipids to body type?

DR ROBERTSON: Could I ask Morris if he has thought of correlating the motor-car habits and the number of miles driven with the incidence of coronary heart disease?

PROFESSOR CRAWFORD: Regarding Morris's observations on the incidence of atheroma in coronary arteries, I would like to comment that I think as a morbid anatomist I would be right in saying that morbid anatomists in the 1908-1913 period were more meticulous observers than the modern ones This is particularly in recording minutiae such as the degree of atheroma in autopsies where it was not a very important feature I think that he should hesitate in assuming because records he examined gave the picture of more advanced disease that there has been a diminution in mural atheroma today

CHAIRMAN: Were those statistics from the London Hospital Pathological Department Dr Morris all in Professor Turnbull's regime or before?

DR. MORRIS: Yes Professor Turnbull He started in 1907

CHAIRMAN: Those all apply to the same regime?

DR MORRIS: Turnbull's Wood s and Russell s - yes

CHAIRMAN: I think that rather removes the objection in these particular statistics, because anyone who has seen the post-mortem reports in the London Hospital will realize they are very uniform

DR MORRIS: Yes and the figures did I think go up until 1956

CHAIRMAN: I hope they are still as uniform as that

PROFESSOR M MICHAEL: This problem of large population surveys in different countries seems to me to bear some relationship to the adequacy of the medical services to the whole population So many of these studies have been based on frequ ncy with which diagnoses are made and very often of course if the surveys particularly in poor rural populations are not nearly so good they are simply not looked at Then there was one great fallacy which I think arose in France - I notice that he had left that off his list - the French doctors were in the habit of it of diagnosing coronary disease only when patients died in the acute episode of myocardial infarction Otherwise it went into the rubbish heap of myocarditis and there were tens of thousands of patients recorded as dying from myocarditis in France which obviously would have been diagnosed as ischaemic heart disease in this country Then one has to take into account the age distribution of population In Uganda they tell me that in the native population a man of forty is an old man and th refore the alleged low incidence in the African natives may be largely or partly the result of the fact that there are very few people who live into the age in which myocardial infarction becomes a possibility or a reasonably frequent probability I think all these things make these population surveys very difficult indeed to assess I was very delighted when I went to Makerere recently to see that Professor Davies has in fact collected and labelled with the age about 700 uncut hearts in which he is waiting for someone to do a controlled study comparing them age by age with the coronary arteries of a corresponding group in a western civilization I do hope that something will be done about that

fairly soon It is a remarkable bit of foresight on his part to restrain himself from further examination of these hearts and wait until a proper comparative study can be made

PROFESSOR MORRIS: I entirely agree with Professor McMichael about the doubtful value of this kind of international statistics and I hope I did not create an impression that I hold by them I left out France intentionally and I left out Portugal Chile, and all these other countries which are usually introduced into these figures, because I have no idea what the deaths from arteriosclerotic and degenerative heart disease mean in Chile, and I suspect that other people who are writing on these equally have not very much idea as to what they mean

In regard to the age distribution there is an important point here, in addition to the one that Professor McMichael made and that is that it is a very queer guy in some of these countries, who survives to fifty This is a problem which has been impossible to tackle It applies too in the West There is a tremendous number of people now surviving from infancy who would not have survived fifty years ago but how to tackle this problem directly or indirectly nobody has been able to suggest Professor Davie s seven hundred hearts - I will not say that it makes my mouth water but it suggests some id as Nervous strain - I would refer you to the recent pap r by Friedman and Ro enman in the Journal of the American Medical Association (1959 169 1286) This paper r pre ents to me a considerable advance on his previous paper It seems to me that it is not so open to so many criticisms as his previous paper and I think it is terribly important; the prevalence of coronary heart disease that he describes in this high pressure group of his this group characterized by competitive striving and meeting d adlines and so forth is remarkably different from his controls however queer his controls may be But it seems to me there is a very important observation there and it is a great shame that this problem has not been tackl d more seriously It is not only a question of blood lipid changes with stress, such as you see before examinations etc but electrocardiographic chang s chang in clotting time changes in arcus senilis and so forth Bodytype - there are everal observation relating body-type to coronary heart disease The first was by Gertl r and White who suggested that m somorphs t nding to fatness w re particularly likely to d velop this disea e and this was confirmed by Spain in his post-mortem study We found among our bu m n that driv rs were fatter or bigg r than conductors right from the start of their career but this does not seem to be correlated with a different experience of coronary h art disease and particularly with a differ nt experience of sudden death from coronary heart disease between drivers and conductors We found that more fat young drivers are liable to sudd n death than fat young conductors middling drivers more than middling conductors and thin drivers more than thin conductors Blood lipids - yes there has been quite a bit of work on that and Tanner s was the last Briti h paper showing that mesomorphs had a higher blood cholesterol and there are sev ral papers on that subject A lot of this work is reviewed in the April issue of the Postgraduate Medical Journal which I would r commend There i an extraordinary interesting collection of data; the whole issue is devoted to th se problems Motor- ars - no it would be v ry very difficult It would hav to be done on an individual ba is I am afraid that we have not attempted that Th se time series are very difficult ev n in much more simple things than coronary atheroma but what I would like to stress that th re is no evidence whatev r of an incr ase in atheroma wh r as there is plenty of vid nce of an increase in occlu ion - of frank thrombosis of myocardial infarction of i chaemic myocardial fibrosis of all the other things The tati tics I put on were more rec nt than for the whole country but if you u e reasonably comparable London Hospital data that is to say

post-mortems carried out by Turnbull Woods and Russell before the first World War - Woods was there from 1911 remember - up to the 1940's you get the same sort of story So what you can draw as an inference from this (and recent work has confirmed it in Germany, I understand) that there is no suggestion whatever of an increase in mural atheroma - indeed it would be fantastic if there was because the population was absolutely stiff with mural atheroma before the first World War and at the end of the nineteenth century If you look through Robert Muir s data in Glasgow around the beginning of the century there is a tremendous amount of coronary atheroma and the same thing is true in the Boston City Hospital from Mallory s data What has changed is occlusi n thrombosis acute infarcts ruptured hearts and all these other things

CHAIRMAN: I would just warn you that talking about statistics, Professor Yudkin has stated that the trend of coronary mortality in this country can be most closely correlated with the number of wireless and television sets that people possess

Some Aspects of the Pathology of Coronary Occlusion

T CRAWFORD

Coronary occlusion used to occur as a complication of syphilitic aortitis but this cause is now rare in this country we see occlusion occasionally - I can remember three or four cases - due to embolism occurring in the course of bacterial endocarditis I have seen two examples due to dissecting aneurysm and one which I interpreted rather hesitantly as thromboangiitis obliterans but for practical purposes coronary occlusion arises as a complication of coronary atherosclerosis and its pathology is a special aspect of the pathology of atherosclerosis in general The general features of the pathology of atherosclerosis have been discussed at earlier sessions of this conference and my purpose now is to take some special aspects of atherosclerosis in the coronary arteries and look at them in more detail

Gross Pathology

Much can be learned about the extent and distribution of disease in the coronary arteries by the use of post-mortem radiographic studies These techniques were pioneered by Gross (1921) and have given much information It is possible to simplify the technique so that it can be used almost as a routine post-mortem study and my colleague Dr Dexter has been doing this for several years

The normal arrangement of the vessels is of interest in 48 per cent of cases (Schlesinger 1940) the right coronary artery is dominant carrying the blood supply for the greater part of the posterior wall of the heart and the posterior part of the septum (Figure 1) in 34 per cent the blood supply to these regions is shared by the right coronary and the circumflex branch of the left and in 18 per cent the right artery terminates at the right border of the heart the left through its circumflex branch being responsible for the whole posterior region There is some evidence that the 34 per cent with a shared circulation are better placed than others as regards ischaemic heart disease and that the 18 per cent with the left dominance are in the worst position



Figu e 1 Post mortem arteriogram of heart showing the right dominant pattern There is stenosis of the left anterior descending artery

Atherosclerosis is usually most advanced in the proximal parts of the main vessels extending for some 5 cm through the left trunk into its anterior descending and circumflex branches perhaps 6-8 cm in the right artery Discrete atheromatous plaques do however often extend more peripherally especially in hypertensive subjects The plaques tend to be localised at points of branching where they give a characteristic appearance of nipping in the x-ray picture (Figure 2) The commonest -



F gu 2 Enlarged post mortem a ter og am how ng nipp ng by an ath o cl otic plaqu at th o gin of a b an h a tery

indeed almost constant - site for advanced lesions is in the first 3 cm. of the anterior descending branch of the left artery and this is often very severely stenosed This is also the commonest single site for complete occlusion though in our material occlusion is only slightly less common in the right artery where it may be either proximal at about 2 cm from the origin or much more distal at about 8 cm Compl te occlusions of the circumflex artery are rather less frequent and are usually situated about 1 cm beyond its origin and it is by no

means rare to find two of the major arteries obstructed - usually one old and one recent occlusion (Figure 3)

With Dr D Teare and Dr D Dexter I have recently been assessing the distribution and extent of disease in the coronary arteries in cases of sudden death attributable to this cause The following table gives some of our preliminary observations regarding the number of arteries severely stenosed

Fatal Cases of Coronary Disease

	Cases showing stenosis or occlusion of		
	1 artery	2 arteries	3 arteries
25 cases aged 50-60 yrs	28 per cent	44 per cent	16 per cent
25 cases aged 20-40 yrs	48 " "	36 " "	8 " "

For the calculation of these figures stenosis has been taken as reduction of the cross sectional area of the lumen to one quarter or less of the apparent normal, assessed by study of serial sections of the stenosed segments which were located by dissection following radiography It will be seen that even with this strict criterion for stenosis, multiple arterial involvement occurs in 60 per cent of the older and 44 per cent of the younger subjects This multiplicity of stenosing and occlusive lesions has been recently stressed by Branwood and Montgomery (1956) while Szilagyi McDonald and France (1958) came up against similar trouble when assessing the applicability of angioplastic procedures in coronary disease

We have found no evidence to support the view which is often expressed that fatal coronary disease in young men is a "different" condition from that occurring in the more usual age group in all these cases young and middle-aged the fatal stenosis or occlusion was on a basis of atherosclerosis as it is usually defined The differences between the two groups are slight and purely quantitative, consisting in general terms of more widespread disease with more extensive stenosis and calcification in the older group than in the younger - though individual members of the younger group have shown just as extensive lesions of all types as occurred in the older group

The Mechanism of Stenosis

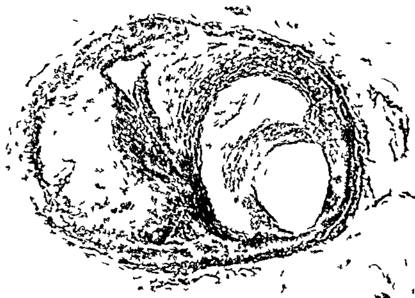
It is not enough merely to state that the stenosis is the result of atherosclerosis for it is common experience that even severe atheromatous disease of the vessel wall often leaves the calibre of the lumen unaffected while at other times - notably in the abdominal aorta and in the basilar artery but sometimes in the coronaries - it even leads to dilatation This variability of the effects which atherosclerosis has on the calibre



F gu e 3 Po t mortem arte iogram showing occlus on of both th left anterio de cending and the right oronary arteri

of the lumen is one of its most perplexing features and in considering it I must recapitulate some of the general features of the atherosclerotic process

The patchy intimal thickenings which are the hall-mark of that process have two constituents - fatty accumulations and dense collagen-like fibrous formations Sometimes the one element and sometimes the other may predominate but both are always represented Examining sections of stenosed coronaries one finds occasionally a zone in which the narrowing results from the sheer bulk of lipid in the wall but much more frequently the narrowing of the channel is associated with great arcs of dense fibres irregularly thickening the intima and reducing the lumen (Figure 4) It is clearly of paramount importance to determine the sources of these two offending substances and *I will consider first the fibrous element which I believe to* be outstandingly the more important in the build up of stenosis



F gur 4 Coronary stenosis resulting from incorporation of succe sive mural thrombi
Stained van G eson X 12

This element received very little attention until 1946 when Duguid expounded what is now commonly referred to as the thrombogenic hypothesis and which Professor Dible has discussed in an earlier paper at this conference To avoid repetition I will limit myself now to stating my view that in the majority of instances significant stenoses result from the incorporation of mural deposits varying in size from slender fibrinous threads to quite bulky coagulation thrombi It is often quite easy to trace successive thrombotic episodes in the thickened intima (Figure 4) though perhaps more often the margins between the deposits become merged in the process of organisation

The origin of the fat in the lesions is less clear to me and there are several possibilities The classical view is the imbibition theory expounded by Aschoff (1924) the fat being regarded as entering the intima from the plasma by a sort of pressure filtration mechanism Alternative views are that the fat arises from the softening of incorporated thrombi from repeated intimal haemorrhages and from the degeneration of elastic fibres There is some evidence that in the early

stages the fat enters the intima by the imbibition mechanism but that later on the other mechanisms are responsible for contributing further fat to the area Small intimal haemorrhages undoubtedly occur (Morgan 1956) and the blood which escapes can be expected to break down to fatty debris while many of the hyperplastic fibres which form in the thickened intima are certainly prone to fatty degeneration (Adams 1959) In my experience however progressive laying down of fat is only exceptionally the cause of the stenosis Fat plays its important part early in the process by inflicting the original damage on the intima and in the great majority of cases stenosis results from repeated deposition and incorporation of thrombi

The Mechanism of Occlusion

Three mechanisms have been mooted for the final closure of a diseased artery thrombosis occlusion by atheromatous debris and intimal haemorrhage Intimal haemorrhage as a cause of occlusion has been much in vogue lately but I remain sceptical regarding its importance In the first place I do not encounter it in my material with anything like the frequency which some workers report and secondly I cannot believe that blood escaping from intimal capillaries could build up sufficient pressure to compress the lumen in which blood is circulating under arterial pressure the haemorrhages occasionally seen probably follow rather than cause the cutting off of blood flow in the lumen

Blockage of an artery by the prolapse of atheromatous debris into the lumen (Figure 5) is an occasional event responsible for a small minority of occlusions - perhaps 5 or 10 per cent It is not usually possible to decide whether occlusion has occurred at the site of rupture or whether the debris has been swept on as an embolus to produce occlusion more distally

The usual mechanism of occlusion is thrombosis in the narrowed lumen and if this is considered in conjun tion with my comments on the mechanism of stenosis it will be realised that the natural history of most of these cases is one of recurring episodes of thrombosis In the earlier stages - when blood is flowing rapidly in the widely patent lumen - the thrombi are small and are rapidly compressed by the blood pressure and incorporated in the wall but as stenosis develops there is the tendency for larger thrombi to form and for incorporation in the wall to be less complete until ultimately occlusive thrombosis occurs But even this final occlusion of the lumen often occurs in several stages and I have been impressed by how often the o cluding plug of fibrin is seen to consist of several component parts of slightly different age (Figure 6)



F gu e 5 Coronary artery occluded by da kly taining atheromatous debris in the lumen
Frozen section sta ned Sudan III and Haematoxylin X 12



Figure 6 Coronary artery occluded by thrombus showing deposition in succe sive zones
Stain d Picro Mallory X 12

Organisation and Recanalisation

Nobody who has carried out systematic examination of the coronary arteries in a large number of post-mortem hearts can be in much doubt about the frequency with which coronary occlusion must occur in the absence of both clinical evidence on the one hand and myocardial infarction on the other survival after occlusion allows the processes of organisation and recanalisation to take place and here a certain element of pure chance seems to be involved for sometimes the lumen is rapidly established by the thrombus retracting away from one side, while at other times recanalisation has to be effected more laboriously by the gradual extension of new channels in from the ends of the thrombus This often results in multiple small channels rather than a single large one (Figure 7) and



Figu 7 Re anal s d orona y a te y with mult ple hann l
Sta ned van G son X 32

it is hard to believe that they can go far to replace the function of the original lumen Furthermore they frequently share the fate of the parent lumen re thrombosis within the new channels finally sealing the vessel off

In conclusion I would stress the role of recurrent thrombosis not only in the final closure but in the build-up of arterial stenosis and also the episodic character of the occlusive lesions with the possible implications this may have in therapy

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Surgıcal Attempts at Treatment

R S PILCHER

Many methods have been devised for the surgıcal relief of angina pectoris and with short term relief of pain as the criterion of success there seems to be little to choose between them The experimental work which I shall describe is based on

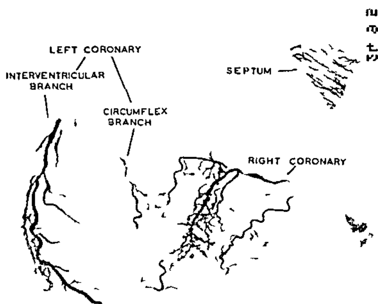


Figu e 1 Post mo tem injection of the h art of a man of 65 w th t n y ar hi to y of angina

the assumption that no treatment of the ischaemic heart will be as effective as one that increases the blood supply of the myocardium This assumption is based on post mortem studies of ischaemic hearts and on the experience of treating ischaemic legs

Figure 1 shows a post mortem injection of the heart of a 65 year old man who died after a surgical attempt to relieve his myocardial ischaemia He had suffered for ten years from angina pectoris of increasing severity lately preventing him from working At post mortem there was no sign of old or recent infarction in the myocardium The right coronary artery was occluded by atheroma at its origin the inter ventricular or anterior descending branch of the left coronary was patent but the circumflex branch was occluded at and a short distance beyond its origin This angiogram was produced by injecting the left coronary artery with a barium gelatine emulsion and it can be seen that the material has filled the right coronary artery and part of the circumflex through numerous intercoronary anastomoses

Figure 2 shows the heart opened out so as to display the coronary vessels without any overlap This shows that in



Figu 2 Sam h art opened out The whole injection has pread from the inte ventricular branch of the left co onary

addition to the surface anastomoses between the right and left coronary arteries there are numerous anastomoses running in the ventricular septum It is clear from this specimen that there are good pathways for the distribution of the available blood and the blood supply was enough to nourish the heart in basal activity but not enough for the extra demands of exertion This is by no means an unusual post mortem finding and by and large the development of intercoronary communications is proportional to the degree of coronary obstruction It is clear from many cases of this sort that intercoronary communications can protect the heart from infarction but may not fit it for hard work Yater et al (1951) found that one third of those who died of coronary disease have no infarction and it is recognised that hard work or emotional stress may precede sudden death in those who suffer from myocardial ischaemia

This situation in the heart is in many ways analogous to that in the lower limbs when they are affected by arterial obstruction Frequently a collateral circulation around an obstruction is adequate to maintain life in all parts of the limb but the total flow may be quite inadequate for exercise In such a case partial relief may be given in many ways but the only way to provide complete relief is to put more blood in the limb Similarly operations to relieve angina pectoris should aim at increasing the blood supply to the heart muscle Merely to stimulate nature s endeavour to produce intercoronary anastomoses does not seem to me enough and in some cases seems to be superfluous

The application to the heart of the successful methods of relieving lower limb ischaemia is technically possible but beset with great difficulties and it is not surprising that surgeons have been more inclined to try less exacting methods One of these is the implantation of the internal mammary artery into the myocardium as advocated by Vineberg (1955)

The experimental work in the Surgical Unit at University College Hospital has been confined so far to a study of the internal mammary artery implant and certain modifications of it Vineberg s claim that the internal mammary artery implanted into the myocardium establishes communications with the coronary arteries has been fully confirmed as also has his observation that more success attends the operation when there is a biological need for it Vineberg s operation has been criticised on many counts of which the most pertinent was expressed in a recent leader in the Lancet to the effect that no one had demonstrated the direction of flow in the implant The flow is in fact in the intended direction from internal mammary artery to heart and it has been possible to make crude measurements of the amount of

flow

Three groups of experiments have been done in the first the internal mammary artery was implanted into normal myocardium and the animals were sacrificed at varying intervals afterwards and studied for the development of communications between the internal mammary artery and the coronary vessels In a second series the internal mammary artery was implanted as before and at varying intervals after the implant the anterior descending branch of the left coronary artery was ligatured Reports of the mortality of this ligature in a normal heart vary widely but all workers are agreed that it is a potentially lethal procedure There seems little doubt from the results that the internal mammary artery implant protected the dog against the lethal effects of the ligature provided sufficient time had elapsed for the anastomoses to form In the third series of experiments the internal mammary implant and the ligature were done at the same time in order to provide the maximum biological stimulus to the formation of anastomoses It was to be expected that a large number of these animals would die and there is no evidence that the internal mammary artery implant provides any immediate protection The procedure at the termination of the experiment was the same in all three series The internal mammary artery was exposed and was divided a few centimetres above its site of implantation into the heart The back flow from the cardiac end of the mammary artery was measured and after death the heart was removed and an attempt made to inject the mammary artery with barium gelatine emulsion When there was a good back flow it was usually possible to fill a part of the coronary system through the internal mammary artery In a few dogs measurement was also made of the forward flow The method employed was crude but allowed comparison of one dog with another without giving a true measure of the flow A polythene coil containing saline in a measured amount was introduced into the divided ends of the internal mammary artery and the rate of displacement of saline by the blood was timed Another method used was the timing of the passage of a small bubble of air through the coil This device introduces considerable resistance and gives an underestimate of the actual flow, the highest forward flow recorded being a little over 3 ml per minute The results in terms of survival after internal mammary implant and coronary ligature are shown in Table I

TABLF I

Internal mammary implant followed by anterior descending artery ligature

13 weeks after implant	2 dogs	2 survived
8 weeks after implant	4 dogs	4 survived
6 weeks after implant	4 dogs	4 survived
4 weeks after implant	6 dogs	1 survived
Same time as implant	12 dogs	5 survived

The numbers in each group are small but the results do suggest that full protection against the ligature is not afforded until some weeks after the implant The mortality in the four week group could be in part due to incomplete recovery from the first operation for there is no doubt that the ligature is more lethal if the animal is anaemic

Injection studies of the hearts of the dogs that survived were of three patterns In the majority of those in which the injection mass entered the internal mammary artery it fill d both the anterior descending and circumflex branches of the left coronary (Figure 3) In a second group the injection passed



F gu e 3 Dog heart nj ctı n of nt rnal mammary implant fill ng both b ancl s of l ft o onary

from the internal mammary into the descending artery only (Figure 4) This result is of some importance as showing that

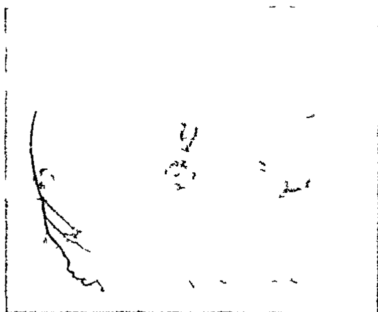


Figure 4 Dog h art injection of nternal mammary artery filling anterior descending branch of left co ona y

survival after ligature is not dependent on pre-existing intercoronary anastomoses which are said to occur in 10 per cent of normal dogs but which I have not yet encountered In a third group in which the injection of the internal mammary artery failed injection of the circumflex artery revealed a rich anastomosis between the circumflex and anterior descending (Figure 5) In no case did the injection enter the right coronary artery Intercoronary anastomoses were clearly best developed in a few dogs in which the internal mammary artery had failed to establish any large communications with the coronary arteries In none of the experiments was any deliberate attempt made to promote the development of intercoronary anastomoses by chemical or mechanical trauma to the myocardium Some of the implants were studied further by microangiography of thin

slices cut across the long axis of the artery Figures 5 and 6 show types of branching demonstrated by this technique



F gu e 5 Dog h a t   nj ction of c r umflex branch of l ft co onary   Th main ana tomotic hannel ove the apex is ut acros

Although these experiments show that the internal mammary artery can provide an additional source of blood to the myocar dium there are two unsatisfactory features in the results the first is the small size of the addition to the coronary blood supply and the second is the time taken for the development of the anastomoses It was thought that a bigger flow might be obtained if a bigger vessel could be implanted in the myocardium In the dog it is possible to implant either the carotid artery or the subclavian with the formation of wider anastomotic channels than occur with the internal mammary implant but neither of these vessels could be utilised in man nor is there any artery readily available of a larger size than the internal mammary An attempt was therefore made to provide a larger channel with a graft from the aorta First a few arterial homografts were tried but these invariably became occluded early



Figure 6 T ansverse mic oangiogram of internal mammary impl nt

and the method was discarded Similar results have been reported by other workers with arterial homografts Secondly a series of vein autografts was started and these are still under study, but the results so far are not promising

Although I think that the internal mammary implant is of value in the treatment of cardiac ischaemia I am sure that we should strive for something better and aim to give the remaining coronary arteries the largest amount of blood that they can handle To this end it seems logical to make use of the methods that have been successful in the leg, namely thromboendarterec-



F gu 7 Transv s mic oang ogram of int rnal mammary mplant

tomy and by-pass grafting The technical difficulties are great but not I would think insuperable Coronary angiography would be of great help and perhaps indispensable in planning such procedures Cannon et al (1959) have published a small series of coronary thromboendarterectomi s and I know of other surgeons who are trying this method

The important conclusion from this experimental work is that it is possible to augment the blood supply of the myocardium from an extra coronary source Although the increment is small and may not meet the demands of strenuous exertion it may afford

some protection against ventricular fibrillation and theoretically is superior to methods which aim only at developing intercoronary anastomoses

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Anticoagulant Therapy

A RAE GILCHRIST

The view is gaining ground that local thrombosis is the dominant factor in the production of occlusive coronary disease Atherosclerosis occurs diffusely and causes dilatation tortuosity and rigidity of the arteries It may persist for years without much harm resulting but the local development of obliterative and stenotic lesions alters the clinical picture and has serious consequences for the individual For practical purposes and whatever the mechanism it is not difficult to advance clinical support for the contention that recurrent local thromboses - perhaps no more than the deposition of successive wisps of fibrin - ultimately transform the relatively benign atherosclerosis into obliterative vascular disease with all its dangers Local occlusions stenoses partial or complete balanced to some extent against compensatory re-vascularisation are responsible for the production of symptoms and gross structural damage

Obliterative coronary disease is a unity with multiple facets overlapping one another and sometimes difficult to differentiate sharply We speak of three groups which in fact often converge - (1) massive infarction the result of gross local thrombus formation (2) minor thromboses microscopic in size - the probable cause of acute coronary insufficiency with pin point areas of tissue necrosis (3) multiple stenoses without infarctions supplemented by subsidiary anastomotic channels sufficient to maintain an adequate circulation at rest but inadequate under the demands of exercise or emotion Local occlusions without infarction are responsible for angina pectoris Accepting the role of thrombosis in determining the onset of occlusions provides a justification for using anticoagulants in all three varieties of clinical coronary disease as outlined above

Acute Myocardial Infarction

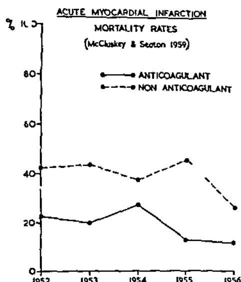
Clinical Studies Most experience has been gained with these drugs in the severest group - acute myocardial infarction Despite a large number of entirely independent clinical studies

yielding remarkably consistent results, the great majority of *investigators who have themselves handled simultaneous control* and treated groups under comparable conditions are of the opinion that anticoagulants are responsible for a reduction in mortality amounting to one-half to one-third of that experienced in the control group during the first month to six weeks of hospital supervision It has not been easy to reach these conclusions the variability in the severity of the attack and in the age distribution being factors of great importance in the immediate prognosis Our clinical experience of anti-coagulants in acute infarction (Tulloch and Gilchrist, 1950) confirmed earlier American work and has been supported by numerous *critical studies since then The immediate mortality rate* and incidence of thrombo-embolic phenomena are significantly reduced

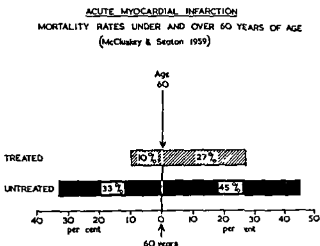
Attempts to assess the value of anticoagulants retrospectively have met with little success and the inferences drawn are far from convincing The difficulties encountered commonly result from the lack of an adequate control series from unavoidable variations in diagnostic standards and particularly from a failure to allow for a changing pattern in the disease process whereby the proportion of elderly patients carrying a more unfavourable prognosis is tending to increase year by year

A striking exception to the inadequate retrospective studies of recent years is the valuable contribution of McCluskey and Seaton (1959) who have analysed the results obtained in two independent medical charges in the Western Infirmary Glasgow over the five year period 1952 to 1956 *Rigid criteria were enforced no case being accepted for* either group unless admitted to hospital within 24 hours of the onset Patients dying within the same period were excluded and only those with pathological Q waves were accepted for study Chance determined the inclusion of the patient in the treated or the untreated group Over the whole five year period the mortality amongst those receiving anticoagulants was 19 per cent against 39 per cent amongst those who did not Similarly although the numbers are small the yearly mortality was consistently in favour of the treated group (Figure 1) The influence of age on the mortality rate is shown in Figure 2 constructed from the data presented by McCluskey and Seaton Over sixty years of age the benefits obtained are appreciably less than under this age though still considerable Thrombo-embolic episodes were reduced from 34 to 18 per cent in favour of the treated group

Pathological Studies The available pathological evidence on



F gure 1 To show the y arly mortality at e over a f ve year p r od n the t at d and unt eated groups r port d by McClusk y and Seaton (1959)



Figu 2 The d g am i const uct d f om th data p es nt d by M Cluskey ar d S aton (1959) It show th nfluenc of age on th mo tal ty ate in th multaneously tr ated and untr at d g oup

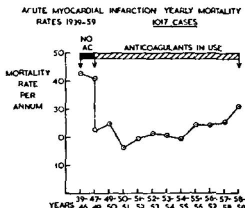
the value of anticoagulants is less convincing than the clinical data Analysing 248 consecutive autopsies performed on patients dying from acute myocardial infarction we (Gilchrist and Tulloch 1956) found little difference in the incid nce

either of intraventricular mural clot or of peripheral infarcts in the two groups of treated and untreated patients In the control group mural thrombi occurred in 36 per cent and peripheral infarcts in 21 per cent as against 32 per cent and 15 per cent respectively of those who had received anticoagulants - statistically an insignificant difference On the other hand the post-mortem incidence of pulmonary infarcts was reduced to 3 per cent in the treated as compared with 17 per cent in the untreated - a reduction highly significant statistically, thus suggesting that anticoagulant therapy even in the least favourable conditions offers some protection to the lungs Lee and O'Neal (1956) emphasize that to inhibit successfully the formation of mural thrombi, anticoagulants must be commenced within three days of the development of the acute infarct

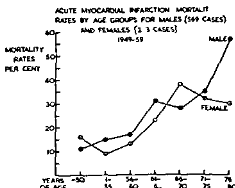
Pulmonary infarcts are deserving of special emphasis They are commonly single, often massive, readily overlooked clinically and radiologically They threaten survival to a greater extent than the usual embolism of a peripheral artery Pulmonary emboli influence both the immediate and the remote prognosis Only one of Cole's (1954) nineteen patients who survived the immediate effects of this complication lived longer than five years The prevention of pulmonary infarction is therefore a major consideration in the successful treatment of acute myocardial infarction

Yearly Mortality Rates My experience of the mortality rates from acute myocardial infarction amongst hospital patients under my personal care during the past twenty years is shown in Figure 3 Anticoagulants were responsible for a fall in the mortality rate by approximately half in the period 1947-49 By 1950-51 the rate had fallen to 16 5 per cent - presumably as a result of the inclusion of a relatively larger number of milder cases referred to hospital by the general practitioner in the hope of active treatment The rate steadied around 20 per cent until 1954-55 since when it has tended to increase and in the year just completed (1959) reached 32 per cent in spite of anticoagulant therapy In point of fact the death rate from acute myocardial infarction in my hospital series is now twice the figure recorded nine years ago The probable explanation is that the age incidence has changed appreciably over the same period of time My hospital charge now receives almost two and and a half times as many patients with acute infarction over the age of sixty years as it did ten years ago whereas the corresponding increase under the age of sixty is only approximately one and a half times greater Age is a dominant factor in determining the immediate prognosis, as shown in Figure 4,

and hence the increased proportion of older people influences adv rsely the over-all mortality rate The pattern of the disease as encountered in hospital practice is changing and the mortality appears to be increasing Retrospective studies on the influence of anticoagulants commonly fail to take this factor into account



F gure 3 Shows th y arly mortal ty rat f om acute myoca d al infa ction among t ho p tal pat ents und r my pe sonal ca e du ng a twenty yea pe iod Desp te the ontinued u of anti oagulants th yearly death rate is now t nding to limb p sumably a a re ult of the latively great r number of pati nts adm tted to the wa ds ove the ag of 60



F gu e 4 To llust ate that the age of th pati nt at the time of the a ut attack is a dom nant factor in determining th imm diat p ognosis

Acute Coronary Insufficiency

This is the term applied to recurrent and prolonged anginal attacks of increasing severity and frequency It is regarded as indica ive of an impending major infarction The justification for using anticoagulants on a prophylactic basis in this group is strong It has been estimated that between

25 and 30 per cent of these patients develop frank infarct formation within a month either of the first onset of symptoms, or of the aggravation of a preceding angina pectoris, in which the frequency of the seizures has been previously fairly constant

So far as I know no strictly simultaneous control and treated series have been studied but Wood's (1959) results are impressive suggesting that the prompt and continued use of anticoagulants may not only ward off the impending infarction, but reduce the frequency and severity of the spontaneous attacks Nichol (1959) treated with anticoagulants 318 patients considered to have symptoms or signs of impending infarction Only 6 per cent did so Personal impressions justify a continuation of this therapy certainly over the acute phase and for two or three months thereafter if not indefinitely

Angina Pectoris

Little is known of the value of long-term anticoagulants in this common condition On theoretical grounds there is much to commend their use The Medical Research Council's anticoagulant working party is now tackling this problem on a long-term basis and perhaps in a few years we may have collected sufficient statistical information to satisfy the critics one way or another

Prolonged Th rapy

On long-term anticoagulant therapy after acute myocardial infarction I would like to make only one or two remarks as the facts are all available for those who would like to study them (M R C Anticoagulant Working Party 1959) The conclusions derived from the preliminary analysis were tentative and we said so Although the difference was not sufficient to be statistically significant in terms of deaths there appeared to be a reduction in the mortality rate in the first six months after recovery from the acute attack There was however a significant reduction in the re-infarction rate for at least two years after the original attack We concluded that phenindione administered continuously to the selected group on whom it was tested can make a useful if limited contribution to the after-care of patients recovering from the acute phase of infarction The evidence in favour of long-term anticoagulant therapy after acute infarction is therefore not complete though very suggestive In Scotland in criminal cases the jury occasionally returns a verdict of "not-proven " which in the absence of all the desirable evidence can be applied to our present experience of long term anticoagulant therapy amongst those with permanent myocardial damage

Summary

Anticoagulants make a real contribution to the treatment of acute myocardial infarction reducing the mortality rate by half in the first four to six weeks of hospital treatment The incidence of thrombo-embolic phenomena particularly pulmonary episodes is significantly reduced

Preventive treatment on a long-term basis is still under trial Complete statistical proof of its efficacy is not yet available but there is at least a theoretical justification for the use of anticoagulants in all three varieties of obliterative coronary diseas

Treatment consists of the oral use of 50 - 150 mg daily of phenylindanedione - or other reliable anticoagulant - in a sufficient quantity to maintain the patient s prothrombin level at two to two and a half times the control figure There is nothing to be gained by expressing this relationship as an index or as percentage activity

The patient's blood should be tested daily at first thereafter perhaps twice or thrice weekly then at two and later at four week intervals

The contraindications to anticoagulant therapy are well known Amongst these hepatic disease diverticulosis and peptic ulceration are worthy of particular note To these should be added a recent major cerebro vascular episode Excluding patients with auricular fibrillation acute myocardial infarction is found in at least 20 per cent of those presenting with hemiplegia or prolonged loss of consciousness Anticoagulants should be avoided in these circumstances

The danger of haemorrhage is real It should not occur with reliable laboratory facilities and close supervision Oral Vitamin K_1 in a small oral dose - 10 to 20 mg - will rapidly correct the bleeding tendency

Anticoagulant therapy is already placing a considerable burden on hospital staffs and laboratory facilities Until some simpler and as effective remedy becomes available there is no satisfactory alternative to this cumbersome form of treatment

Acknowledgments

I am indebted to Dr McCluskey and the Editor of the Scottish Medical Journal for permission to reproduce Figure 1

Figure 2 is constructed from the data reported in the same paper

R E F E R E N C E S

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The Laboratory Control of Long-Term Anticoagulant Therapy

ROSEMARY BIGGS

The evidence is accumulating that anticoagulant therapy is of benefit to patients with coronary thrombosis both as a short term treatment and when given for long periods of time The safe use of these drugs r quires skilled laboratory work and a good co-ordination of the various services The wide acceptance of long-term anticoagulant therapy would raise very considerable problems for the National Health Service Although these prob lems may not be thought to be the direct responsibility of the physician the safe treatment of patients depends largely on everyone concerned giving due thought to the questions which arise

We calculated that if all of the patients now treated in the Oxford area on short term anticoagulant therapy were transferred to long-term therapy we should soon have over 1000 patients undergoing such treatment at any one time By sheer magnitude this would soon involve additions to staff and recon sideration of the organization

The two main problems which arise are

(1) the choice of the laboratory method and

(2) the best organization

The Method of Controlling Results

A large number of different methods have been used for the laboratory control of anticoagulant therapy but only one has gained any wide acceptance in this country This is the one-stage prothrombin time This method has the advantage of extreme superficial simplicity Any laboratory assistant can do this technique and get apparently reproducible results with practi cally no practice at all The reagents are commercially prepared or simple to make Detailed study does however reveal that the method is not nearly so reliable as first acquaintance suggests The results of different laboratories are often not the same and there is a wide random variation in the results which means in practice that great reliance cannot be placed on single observations For long-term therapy this is a grave disadvantage when a patient has one investigation a

month much reliance must necessarily be put on the single reading in planning future dosage For these reasons I feel fairly certain that the unmodified one-stage method is unlikely to be adequate for the control of long-term therapy

The only practicable tests with much advantage over the ordinary one-stage method are the modifications devised by Owren The first of these modifications is technically much more tiresome to do than the unmodified test Special reagents have to be prepared in the laboratory and accurate dilutions have to be made It is not a method that could reasonably be done in a small laboratory containing no one with any special interest in blood coagulation Thus if this method were adopted the problem of centralised testing laboratories for an area would arise

The second modification is primarily designed for use with capillary blood but can also be used with venous blood It is very easy to do but requires a special reagent which has to be bought from Norway This method is not quite so reliable as Owren s original method but is well within the scope of all small laboratories

The choice of laboratory methods is not the primary concern of the physician but failure to realize that some methods are much better than others may greatly reduce the safety and efficiency of treatment

The Organization of Laboratory Services

With our present system of organization in Oxford we are constantly faced with a triangular difficulty in communications The patient sees the physician and then comes to the laboratory for testing By the time that the testing is complete the patient has departed for home and the physician has left the clinic The results have therefore somehow to be transmitted to the physician and thence advice has to be transmitted to the patient

In some centres this difficulty is partially overcome by the pathologist taking the responsibility for controlling dosage This is an individual arrangement and probably not a very wise one as a general rule The pathologist is unlikely to be aware of all the special medical features of each case

In Norway the reverse organization has been achieved The medical and laboratory services are run together and the laboratory testing is done essentially in the clinic This again is not universally applicable because relatively few physicians would wish to be directly responsible for a testing laboratory

In most instances a compromise arrangement will have to suffice For example it might be possible to organize medical

clinics in the afternoon so that laboratory testing is done in the morning and all of the results are available by the time the patient arrives Or the tests might be done on samples sent by post during the previous week

Conclusion

These very domestic details are probably not very interesting But domestic details have a habit of being very important Moreover I am sure that now is the time for this whole problem of a co-ordinated service for anticoagulant therapy to be discussed Unless detailed plans are made the widespread introduction of long-term therapy is likely to cause a breakdown of the existing pathological services

DISCUSSION

PROFESSOR McMICHAEL: Experience with the antiprothrombin drugs has been satisfactory to most observers in reducing the incidence and severity of venous thrombosis and pulmonary embolism It is still debatable whether it reduces the frequency of further extension of infarction in the acute stage of coronary occlusive disease The enormous variability of mortality in the acute stage of infarction in reports from different centres indicates the immense difficulties in choice of controls for such studies I shall therefore confine my remarks to long-term "anticoagulant" therapy of survivors from the acute stage where there is a much greater uniformity of opinion about prospects and prognosis

The M R C 's influential working party deserve great credit for their report on a trial of long-term treatment Close study and thought however reveal that some of their documented results are capable of a different interpretation Better survival rates in the treated series in the early months tended to vanish to statistical insignificance as the trial went on Most statisticians would interpret this as indicating that chance had been responsible for the earlier hopeful results or that a far greater number would be needed to iron out the great variations possible in the material The working party's decision that benefit was limited to the first six months in younger subjects is difficult to square with accepted ideas on pathology If the treatment prevents thrombosis why should it cease to do so and why should it fail to work in older subjects? The longer term mortality difference though slightly favourable to anti-coagulants" is too small to be convincing

Much emphasis was also laid on the higher incidence of recurr nce of infarction in the control s ries but most clinicians are aware of the great difficulty of interpreting post-infarction pain It is notable that there was a higher fatality rate from recurr nt infarctions in the treated group (17/24 with 7 survivors) while the greater number of survivors (32/60) of recurrence among the untreated were on follow-up apparently little the worse as they were no more dyspnoeic than their treated counterparts

Protagonists of long-t rm anticoagulant therapy are also far from uniform in their ideas about prevention of recurrences and the applicability of the treatment Toohey for example, had 67 per ent of r currences in his treated series against 20 per cent in his controls while Suzman found comparable frequencies of recurrences in treated and untreated though less fatal in the former: this contrasts with the opposite findings of the M R C Though these authors' studies were statistically poorly planned their exp rience is relevant and quite the opposite of the M R C findings Toohey claims good results in recurrent infarction, while Bjerkelund claimed no significant benefit in this type of case Advocacy of long term anticoagulants is thus support d by the most varied and confused arguments

For thirty years we have been able to make a positive diagnosis of myocardial infarction with a high degr e of accuracy and we cannot afford to neglect the massive a cumulation of

experience and the very full and accurate studies of prognosis in survivors of the acute attack made in this country in the U S A and in Swea n Advancing age worsens the prognosis and younger patients have much better survival prospects in terms of years If we confine our elv s to the prospects of those who have survived the acute phase of a single infarction before the age of 65 there are excellent available reports (numbers of patients in brackets) from Biörck et al (685) Cole et al (285) Morris et al (119) Palmer (212) Robb and Marks (166) Sigler (1147) and Waldron and Constable (1551) covering 4 165 patients The remarkable thing about these reports i their uniformity giving a prospect of survival at fiv years of 61 to 75 per cent One very remarkable series was that of Morris on 119 doctors who had a 78 p r cent five year survival after the first episode We can uperpose on t a survival curves of this large untreat d material the results claimed from tr atment Neither Bjerkelund s nor Suzman s results show any improvement in prospects of expected survival as compar d with this very large experience of prognosis in untreated patients

Long-term treatm nt with "anti oagulants is far from harmless as we have already seen in the papers in this symposium from Drs Marshall and Shaw Haemorrhage sometimes severe is fr quently reported In 119 cases Bjerkelund had 4 deaths from c rebral haemorrhage and Fuller has recently reported 2 (?3) deaths from Newcastle

I submit therefore that the evidence of benefit in prev ntion of further coronary occlusion i to say the least very weak We have seen the great complexity of the pro esses of occlusive arterial di ease from Professors Crawford and Dible Dr Poole has shown that even heparin does not prev nt the initial phases of thrombosis Our pr sent m thods of approaching the problem may be unsound Even if "anticoagulants" limit thrombus formation such benefit could theoretically be off et by subintimal haemorrhage R placement of coronary thrombosis by cerebral haemorrhage is tragic At present we can only express our appre iation of the efforts of those of our colleagues who are trying to tackle this very difficult problem and from them we must expect further and we hope more decisiv evidence Our present prophyla tic efforts have largely failed nd in view of these disappointing re ults post infarction patients hould not be subjected to long continued m di ati n which keeps th m in a state of fear of clotting on the one hand or bleeding on the oth r Good general medical care (such as doctors appear to be able to give themselves) seems to give better results than a trouble ome regime which extends invalidism and adds to the anxi ty of both patient and doctor

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CHAIRMAN: This is open for further discussion I think McMichael has drawn attention to a point that has always puzzled me in this statistical life saving - the enormous increase in mortality in the controls In our series that he has referred to published thirty years ago we found the incidence of clinical embolism eight per cent and if you add the two or three cases of venous *thrombosis, it makes eleven per cent* Shortly before anticoagulants were used Blumer analysed a very large number of cases from different sources and he found the incidence of clinical embolism eleven per cent Within a few months almost of anti-coagulant therapy it had shot up to 26-28 per cent in the controls and I have never been able to understand that I would like to hear other people's views and I would simply say at this stage that I do not use anti-coagulants myself as a routine in acute myocardial infarction I use them in selected cases, and I have an entirely open mind on the long-t rm therapy

SIR GEORGE PICKERING: McMichael has presented a very able criticism of the report of the Medical Research Council Working Party of which I had the privilege of being Chairman I am in a slight difficulty here because I have not looked at the report or at the figures for some months whereas he has obviously made a very close study of it But he claims that he has no emotional bias in this, and I wonder very much why the evidence he produced so strongly was that of Suzman and Toohey whose papers he has criticiz d later The best evidence I think before the Medical Research Council Working Party was that of Bjerkelund from Oslo whose findings were very much the same as that of the Medical Research Council Working Party He has said that he thought 'the unkindest cut of all' was our reply to him that if we erred we erred in the interests of our patients and I think he ought to know and you ought to know that people doing a controlled therapeutic trial are very exercized about the ethical aspects of the trial They do not really like to feel that they are doing their patients any harm We saw this yesterday when the reports of the trials on anticoagulants and cerebral vascular disease came along: there came a stage when those responsible became unhappy about the ethics of going on Now what happened to us in this trial was that there came a stage when the statistician reported to us that the deaths amongst those in whom anticoagulants had been withheld were statistically significantly greater than those in which anticoagulants had b n given And we felt that with this knowledge we were not justified in the patients under our control in withholding anticoagulants Now this as it turr ed out was rather unfortunate because when the results finally were analysed although more patients died in the series in which anticoagulants were withheld than in those in which anticoagulants were given the difference was not statistically significant Here let me remind you of what these things mean A treatment at one end can save every life; at the other end it can kill everybody and in the middle it does nothing at all Somewhere between that the treatment may do a little good and it may do a little harm What is generally regarded as statistically significant is that that result may be expect d to happen more than nineteen times out of twenty and that was the difference between this mortality - there was a differ nce in mortality but it was not statistically significant Now what was statistically significant was the recurrence of infarctions particularly in the fir t few months after the first one And that has been quite justifiably criticized in that this could have been influenced by the preconception of those taking part in the trial; that I think is perfectly true and there is no getting away from it I think that what this trial showed was that if anticoagulants contribute to the survival of patients and if they prevent recurrent thrombosis this contribution *is a modest one We thought it* was real we did not go on with the trial for the reasons I have stated to you; but fortunately there are other trials being done

in other countries and I hope that some time the evidence will come together

DR TOOHEY: As Professor McMicha l has quoted me I would like just to clarify one point - one important point - he quoted some figures in a paper that I published last year about the question of recurrent infarctions; 66 per cent in the treated group and 19 in the untreated group This is perfectly correct As point d out in that paper this was not it was clearly stated a yn-chronous controlled trial The controls were taken retrospectively from patients admitted to the same hospital before I started treating patients with long-term treatment and al o the larger number of cases were those patients from a similar hospital in the same area and with the same type of patient admitted Now in this group these were all the patients admitted whereas the pati nts that I had treated w re only the more severe cases I did not treat the cases who just had survived one acute infarction and who seemed to have made an almost complete recovery I only felt justified at this time in treating those patients who had had two or more infarctions or who had a very evere infarction associated with heart failure Therefore the treated group were not a synchronous control group but they were a v ry mu h more s vere group and therefore one would have expected the mortality rate in thi treated group to have been greater than the control series In fact the mortality rate was lower All trials have difficulties and esp cially any trial that is not a synchronous control trial is greatly open to question I did not produce valid conclusions from this I merely stated that I thought that long-term anticoagulant therapy was of value it merit d further trial and that is the same opinion that I have today

I would like to ask one question from Dr Gilchrist or Dr Bigg or anybody else in the audience and that i the question of the degree of control of anticoagulant therapy Has anybody assessed long-term anticoagulant therapy in relation to the adequacy of the control? Anticoagulant therapy is far from a simple procedure It takes consid rable skill to maintain adequate treatment day in day out over the years In my own clinic wh re I had over .00 patients on long-term treatment I consider that not more than 85 per ent of patients were having adequate anticoagulant treatment This in spite of the fa t that one p rson namely my elf prescribes the treatment and i in charge of the supervision of the laborat ry control and seeing the pati nts personally at the time they att nd Even so I consider only about 85 per cent of the pati nts are having adequate control Now in an analysis of more than 180 patients who have been on long-term anti oagulant therapy for at least six months and the vast majority for over a year the inciden e of recurrent thrombo- mbolic epi ode i four times as great in the patients who ar con idered to have had inadequate control I wond r whether Dr Gilchrist or anybody else bears out th e figures

DR RAE GILCHRIST: I can an wer that ery quickly S far as our personal cases of long-term th rapy are conc rned we have not assess d the results obtained in r lation to the degree of control of the prothrombin time It is a v ry important point and it is an a pect of things which the Anti-Coagulant Committee has alr ady consider d and which we are turning over in our minds mind

PERIPHERAL VASCULAR DISEASE

Chairman—Sir George Pickering

Investigation of Peripheral Vascular Disease

LAWSON McDONALD

I intend to restrict my remarks to patients presenting with either intermittent claudication or with gangrene of the lower limbs and to consider which investigations are useful in the investigation of such patients If severe anaemia embolism and coarctation of the aorta have been excluded atherosclerotic occlusive arterial disease is the underlying cause in the vast majority of cases Rarer causes that have been found include polyarteritis nodosa external pressure on an artery by a tumour elastosis dystrophica and xanthomatosis Current experience is that thrombo angiitis obliterans is a very rare condition cases with atherosclerotic arterial disease are often wrongly given this diagnosis Abnormalities of lipid metabolism and of blood coagulation and thrombosis are likely to be as important as in ischaemic heart disease (McDonald and Edgill 1959) with regard to the whole group of patients with occlusive arterial disease of the legs but are at present of limited importance in the investigation of the individual patient It is however important to realise that any patient presenting with peripheral occlusive arterial disease is likely to have ischaemic heart disease in addition and possibly occlusive arterial disease elsewhere

Special investigations may sometimes be needed to confirm the diagnosis in the early case or they may determine the anatomical extent of the lesion and the degree to which it has impaired the circulation But in order to see special investigations in peripheral vascular disease in their true perspective it is important first to consider the salient clinical features of occlusive arterial disease Physical signs are usually late in onset in the course of peripheral occlusive arterial disease the early case is singularly lacking in signs and may particularly need special investigation for diagnosis

In the affected part important changes may occur the skin is dry and poorly nourished it sweats little and is deficient in hair and the nails are atrophic The muscles of the calf and sometimes those of the thigh and buttock depending on the

level of arterial obstruction may be wasted This local muscle wasting in occlusive arterial disease with local ischaemia seems analogous to the generalised muscle wasting which may occur in conditions associated with a low cardiac output The limb, especially its periphery may be blue or pale It may blanch on elevation The soles of the feet may become pale in contrast to their normal pink colour after exercise by dorsiplantar flexion with the patient lying horizontal and the leg elevated to 45 degrees As the palpating fingers are passed distally the limb is found to become cold indicating the level of arterial obstruction Ischaemic muscles are sometimes tender to palpation Pulses may be absent or poor in volume but sometimes they are normal at rest in the presence of significant occlusive arterial disease

Occlusive arterial disease may reduce the flow of blood through the skin and lead to gangrene or cause intermittent claudication by reducing the muscle blood-flow (Figure 1) Special investigations are designed to demonstrate the arterial occlusion or to measure blood flow through the skin or to gauge muscle blood flow

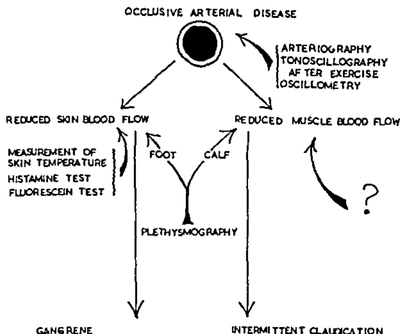


Figure 1 See t xt Reproduced from McDonald L and Semple R (1952b) by courtesy of the Honorary Editor of the Proceedings of the Royal Society of M dicine

Aortography arteriography tonoscillography after exercise and oscillometry give information about the actual site of arterial occlusion or narrowing and will be referred to later Straight radiographs are of little value arterial calcification is frequently medial and unrelated to intimal atherosclerosis Various tests can be used to measure skin blood flow in luding the measurement of skin temperature by a suitable thermometer the histamine test and the fluorescein test However significantly reduced skin blood flow is usually readily apparent at the bedside Plethysmography has been of great value for research purposes when applied to the foot it reflects skin blood flow and to the calf muscle blood flow No satisfactory method has been found for the easy measurement of muscle blood-flow clinically although for experimental purposes the clearance of radioactive substance the measurement of oxygen tension by a polarograph (Montgomery 1957) and the use of thermocouples have been employed Aortography may be performed by the injection from the back of a radio opaque dye directly into the aorta under general anaesthesia Alternatively the dye may be injected into the aorta via a catheter introduced through a femoral artery Aortography played a very important part in helping to identify and separate aortic and iliac arterial occlusions from those in the limbs (Kekwick McDonald and Semple 1952) Arteriograms are obtained by taking serial radiographs of the thigh and leg after percutaneous puncture of the femoral artery and injection of radio-opaque dye The technical details of aortography and arteriography have been frequently described and I do not propose to go into further details now

Tonoscillography after exercise (Ejrup 1948) has proved to be of diagnostic value Although a special method of investigation in the first in tance it has helped the physician to gain more from the purely clinical examination of the patient (McDonald and Semple 1952a 1952b) The tonoscillograph is an automatic oscillograph A cuff placed around the limb is automatically inflated and deflated with compressed oxygen and pulsations in it during the inflation phase are transmitted by means of a piezo-electric manometer and an amplifier to a pen As the pressure increases the pen advances vertically and pulsations are recorded in the horizontal plane The recording paper is marked with horizontal lines and the apparatus calibrated so that these mark the increase of pressure in the cuff from 0 to 300 mm Hg A tracing is automatically obtained every 30 seconds The particular value of tonoscillography after exercise lies in the graphic registration of arterial pulsation after exercise In atherosclerotic occlusive arterial

disease pulses which are present at rest may become temporarily impalpable after exercise The patient rests quietly on a couch covered with a rubber mattress for fifteen minutes The cuff is then applied at the ankle After a satisfactory record at rest the subject exercises either by dorsiplantar flexion of the foot for 90 seconds while lying horizontal or by running gently or by walking briskly for up to 200 yards In normal people the amplitude of arterial pulsation increases after exercise (normal response) (Figure 2) whereas in occlusive

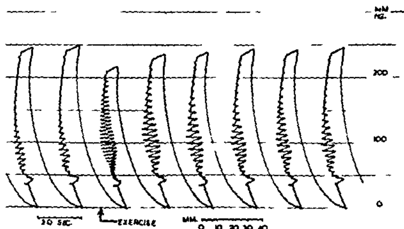


Figure 2 Tonoscillogram from the right thigh of a normal person showing increased pulsation after exercise Reproduced from McDonald L and Semple R (1952a) by kind permission of the publishers of the British Heart Journal

arterial isease with either complete or incomplete obstruction it diminishes (inverse response) (Figure 3) This inverse response lasts for at least two tracings after exercise and may persist for as long as thirty minutes Subsequently readings are similarly obtained at the calf and thigh and sometimes at the foot The site of arterial obstruction demonstrated by arteriography and the level of the inverse reaction agree well and the more proximal the arterial obstruction the more proximal will be both the symptoms and signs The inverse reaction occurs distal to the site of gross narrowing or obstruction of a vessel and persists distal to that site and therefore only the most proximal limit of obstruction is defined

Diminished arterial pulsation after exercise can frequently be clinically detected The dorsalis pedis and posterior tibial pulses are palpated after rest and their position marked with a skin pencil The patient then exercises In the great majority

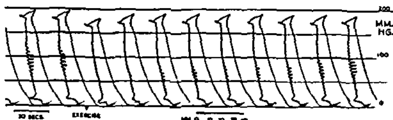


Figure 3 Tonoscillogram f om th r ght ankle of a pati nt w th intermittent claudication due to occlu ive arterial disease showing decreased pulsation after ex rcise Rep oduced f om McDonald L and S mple R (1952a) by kind permiss on of the publi hers of the Br tish Hea t Jou nal

of patients with arterial obstruction the pulses will be impalpable after exercise or they will become greatly diminished for ½ - 3 minutes This bedside test is sufficiently sensitive to detect an inverse reaction in the majority of cases Although Andre-Thomas and Levy-Valensi described this clinical phenomenon in the French literature in 1918 its diagnostic value has not been generally appreciated

In conclusion past research has made special investigations unnecessary in the majority of patients with peripheral occlusive arterial disease although arteriography or aortography is important before any direct surgical measure

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Role of the Sympathetic in Peripheral Vascular Disease

H BARCROFT

My task is to speak about the role of the sympathetic in peripheral vascular disease and particularly in occlusive arterial disease as commonly occurs in the lower limbs The sympathetic is important in connection with the treatment Patients with occlusive arterial disease are often treated by lumbar sympathectomy The value of sympathectomy must be judged by its results Whether or not it has a rational basis is really a matter of only secondary importance But the rationale is of some interest And in this connection the physiologist may be asked some questions As for example "What effect would sympathectomy be expected to have on the blood supply to the toes? Could it relieve intermittent claudication? How would it affect the collateral circulation?"

First the toes N D Royle (1924) performed the first lumbar sympathectomy for the relief of spastic contraction of the leg muscles he noticed that the patient's toes were much warmer after the operation This was confirmed by Adson & Brown (1929) who found that the rise in temperature lasted for many weeks Lynn & Barcroft (1950) recorded the temperature and foot blood flow daily before and after sympathectomy They too confirmed the rise in temperature of the toes This persisted although the post-operative increase in flow in the foot had subsided to about double its preoperative value (Figure 1) The explanation of the persistent rise in toe temperature is not settled At first it is due to the marked increase in blood flow resulting from the removal of sympathetic vasoconstrictor tone from the digital arteries, arterioles and arteriovenous anastomoses But as days pass intrinsic tone develops and hyperaemia subsides to some extent Other factors which may favour the prolonged rise of toe temperature are the absence of sweating and the loss of venous tone (Goetz 1950) In cold weather the circulation through sympathectomized toes will be better than that through normal ones as the vessels will not be subjected to strong reflex vasoconstriction

Now as regards the skin of the legs It is a striking

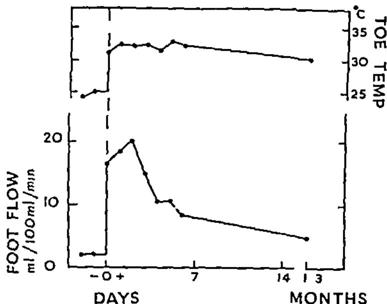
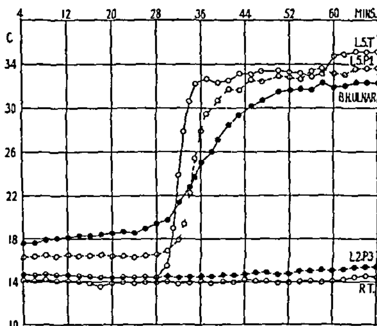


Figure 1 Results showing that sympathectomy is followed by a prolong d rise in the temperature of the toes although the hyperaemia in the foot subsides (plethysmograph)
Broken vertical line sympathectomy
(Walker Lynn & Barcroft 1950) (By kind permission of the Editor St Thomas's Hospital Reports)

fact that sympathetic control of the circulation in the skin of the legs is much weaker than that in the toes Whereas ulnar nerve block is followed by a large rise in finger temperature little or no rise in the temperature of the skin of the limbs is seen after blocking cutaneous nerves (Lewis & Pickering 1931 Figure 2, Grant & Holling 1937) It is not likely that sympathectomy would be followed by much increase in the skin circulation in the legs The sympathetic probably constricts these vessels a little in the cold (Roddie Shepherd & Whelan 1957) so in the cold the circulation through the skin of the sympathectomized leg might be improved

To turn now to the skeletal muscles The effect of sympathectomy on the circulation through the upper part of the forearm which is mostly muscle has been studied by Grant & Pearson (1937) and by Duff (1951) Both used the venous occlusion plethysmograph Daily measurements of forearm flow before and after cervico-dorsal sympathectomy revealed a post-operative increase in flow returning to normal within a week (*Figure 3*) We have seen that the sympathetic maintains very



F gure 2 Results showing that sympathet c va oconstrictor tone is strong in the fingers
Left ulnar nerve block followed by rise in temperature of the ulnar border of the hand and of the p oximal and terminal phalanges of the fifth finger (L5T L5P1 B H Ulnar)
(Lewis & Pickering 1931) (By kind permission of the Ed tor Clinical Science)

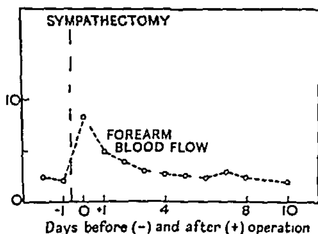


Figure 3 Results show ng that sympathectomy is followed by a transient increase in the blood flow in the forearm (Plethysmograph) (Duff 1951) (By kind permission of the Editor Clinical Science)

little vasoconstrictor tone in the skin proximal to the wrists and ankles so that the transient post-operative increase in flow in the forearm is likely to be deep to the skin probably in the skeletal muscles Barcroft Bonnar Edholm & Effron (1943) showed that blocking the deep nerves of the forearm increases blood flow through the skeletal muscles due to the release of sympathetic vasoconstrictor tone in muscle vessels This has been confirmed (Roddie Shepherd & Whelan 1956) We can infer that lumbar sympathectomy would probably release sympathetic tone in the skeletal muscles of the legs But the increase in flow would last for less than a week It seems unlikely that lumbar sympathectomy will be followed by very lasting improvement in the circulation through the resting muscles of the legs

So much for the effect of sympathectomy on the circulation in resting muscles Would it be likely to improve the circulation to exercising muscle? Might it relieve intermittent claudication? This seems unlikely The evidence is as follows Grant (1938) studied the effect of a standard exercise on the blood flows through a normal and a sympathectomized forearm The exercise was clenching a bar with the hand as hard as possible for one minute The post-exercise hyperaemia in the sympathectomized forearm was the same as that in the normal forearm (Figure 4) In spite of disconnection from the vasomotor centre the vasodilatation in the muscles of the sympathectomized limb developed and subsided perfectly normally Grant attributed it to the action of vasodilator metabolites I am indebted to Dr J S Paddle (19,9) for further evidence that the sympathetic innervation of the leg muscles seems to be of little or no significance in a quarter-mile race A healthy policeman aged 26 years came into St Thomas s Hospital under Professor J B Kinmonth for bilateral lumbar sympathectomy for hyperhidrosis of the feet The day before operation his times for two all-out runs one in the morning and one in the afternoon over a distance of 383 yards were 65 and 61 sec On the 99th day after operation under quite similar conditions over the same course his times were 60 and 62½ sec The gratitude of the patient for his dry feet and his comment on the increase in moisture of the skin of the upper part of his body were indications of the success of the operation But the absence of the sympathetic supply to his leg muscles made no difference to him in a quarter-mile race Clinical experience too provides further evidence that sympathectomy has no effect on the circulation through exercising muscle Evidence that is not expressed in graphs or experimental results but nevertheless is most significant It is as follows Many sympathec-

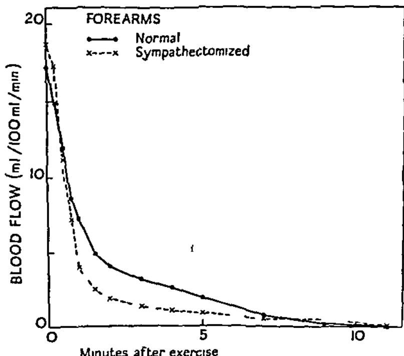


Figure 4 Results showing that sympathectomy has little or no effect on post exercise blood flow
The subject clenched a bar and released it at time O
Continuous line Normal forearm
Broken line sympathectomized forearm
(Grant 1938) (By kind permission of the Editor Clinical Science)

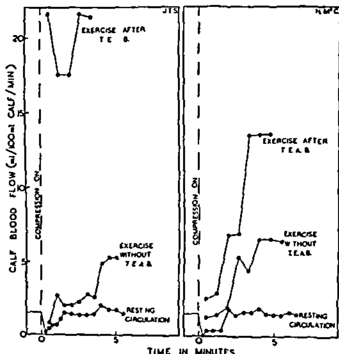
tomies have been performed on young and active subjects of both sexes for the relief of hyperhidrosis So far as I am aware no loss of muscular faculty has ever been noticed Loss of muscular faculty is never even considered as a possible contra-indication to this operation Surely this must mean that the role of the sympathetic supply to human muscle vessels during exercise is a negligible one even in active subjects in the prime of life Whether or not their muscles have sympathetic fibres makes no noticeable difference to walking, running swimming tennis etc etc The results of clinical experience are in accord with those of Grant and of Paddle and I think prove that sympathectomy will have no effect on the circulation in exercising muscle

There have of course been other views Since sympathectomy improves the circulation to the toes it has been advocated for intermittent claudication in the belief that it might improve the circulation to exercising muscles However this is

very unlikely in view of what has already been said It is indeed quite easy to cite experiments where results suggest that sympathectomy might actually cause a loss of faculty in exercise Folkow Uvnas and others have shown that hypothalamic stimulation in cats causes acceleration of the heart and other changes associated with exercise including marked vasodilatation in the skeletal muscles mediated by the sympathetic (Eliasson Folkow Lindgren & Uvnas 1951) *The sympathetic may open the* muscle vessels in exercise - at any rate in the cat In man the sympathetic increases the blood flow through resting muscle in stress The human results are based on plethysmographic experiments on subjects who have been deliberately frightened or made to do rapid mental arithmetic (Brod Fencl Hejl Jirka & Radlafousek 1958 Blair Glover Greenfield & Roddie 1959 Blair Golenhofen & Seidel 1959) From these results it appears that sympathectomy might do harm in exercise by abolishing seemingly useful vasodilatation But in fact clinical *experience and the experiments of Grant and Pearson* and of Paddle fail to show any significant function for the sympathetic supply to human muscle in exercise

Lumbar sympathectomy would abolish the vascular responses in human skeletal muscle that occur during stress (Blair et al 1959) and also the responses which have been found during fainting (Barcroft Edholm McMichael & Sharpey Schafer 1944) and during changes in body posture (Brigden Howarth & Sharpey Schafer 1950 Roddie & Shepherd 1956) It seems unlikely that the abolition of these responses in arteriosclerotic legs would matter to the patient

To turn now to the effect of sympathectomy in the collateral circulation Dornhorst and Sharpey-Schafer (1951) have shown that sympathectomy is followed by increase in flow through collateral vessels but only for a few days Shepherd (1950) too found that the sympathetic supplied and tonically constricted the collateral vessels of the hip His method is interesting He measured the rate of the blood flow through the calf of a normal subject after exercise performed during occlusion of the femoral artery in the groin In these circumstances peripheral resistance in the calf is very low and the main resistance is in the collateral vessels near the hips To see if the sympathetic supplied and maintained tone in these vessels calf flow that is to say collateral flow was measured as described both before and after the administration of the adrenergic blocking agent tetraethylammonium bromide (TEAB) Following the injection of TEAB calf blood flow i e collateral blood flow increased (Figure 5) The inference was that the sympathetic supplied the collateral vessels and mediated vasocon-



Figu e 5 Results show that the sympathetic maintains vasoconstrictor tone in the collateral v ssels of the hip
For explanation see text
(Shepherd 1950) (By kind permission of the Editor Clinical Science)

strictor tone The transient increase in collateral blood flow found after sympathectomy by Dornhorst and Sharpey-Schafer is probably due to disconnection of these vessels from the vasomotor centre It is unlikely that sympathectomy would cause a lasting improvement in the collateral circulation Intrinsic tone develops quickly in these vessels and the rate of the circulation very soon is back to normal

So far as I am aware nothing is known about the action of the sympathetic on the blood vessels in human bone Bone blood flow is very small The release of any vasoconstrictor tone in the bone vessels would scarcely alter the blood flow in the limb In the cat sympathectomy increases the circulation in bone marrow (Herzig & Root 1959) Nothing is known about the recovery of intrinsic tone after sympathectomy in the vessels in human bone

To sum up the effects of sympathectomy on the circulation in normal limbs are as follows There will be a long-lasting improvement in the circulation in the toes There will not be so much effect on circulation through the skin of the legs

possibly a little improvement when the subject is cold The collateral circulation and the circulation through the resting skeletal muscles will be improved for a few days only after which it will return to its pre-operative rate There will be no effect on exercise The effect on the circulation in human bones is unknown

In occlusive vascular disease if the vessels can dilate the most important result of a sympathectomy is likely to be a long-lasting improvement in the circulation in the toes Our knowledge of the effects of sympathectomy is still incomplete Clinical experience alone must decide the place of sympathectomy in the treatment of occlusive arterial disease

The reader may find the following references of interest
Sympathetic denervation Barcroft & Swan 1953 Monro 1959
Escape areas Monro 1959
Intrinsic tone Burn & Rand 1959
Sprouting Murray & Thompson 1957
Dual circulation in muscle Barcroft & Dornhorst 1954
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Peripheral Vascular Disease in Diabetes

W G OAKLEY

The relationship between arterial disease and diabetes is more easily assumed than proved It cannot however be denied that atherosclerosis occurs at an earlier age and tends to be more severe in some diabetics than in the general non-diabetic population In spite of the absence of any characteristic histology the view has been put forward by Lundbaek (1954) that in diabetes there is a specific form of angiopathy this is based on such considerations as the sex incidence of coronary artery disease associated specific vascular lesions in the eyes and kidneys and small differences in the lecithin and cephalin content of the arteries affected Long-standing diabetes is not however necessarily associated with or complicated by atherosclerosis in a series of 816 autopsies reported by Warren and Le Compte (1952) 66 were described as being free of aortic atheroma In this connection I would like to say that in the course of one week I recently saw three women all of whom had had diabetes for approximately 35 years and showed no evidence of arterial or other complications

It is important to remember that in haemochromatosis arterial disease is no more common or severe than in normal subjects of comparable age this perhaps does no more than demonstrate that a raised blood sugar level does not appear to play a major role in the production of arterial disease It is interesting to note that diabetic retinopathy and nephropathy are complications virtually unknown in this disease

The influence of diabetic control on the incidence of atherosclerosis has been the subject of numerous studies but conclusions based largely on clinical evidence lack general agreement Duration and severity of the diabetes have received similar consideration and the former generally regarded as bearing a closer relationship than the latter to arterial disease Particular attention has been paid to the more specific arteriolar and capillary lesions in the retinal and glomerular vessels in cases of long-standing diabetes and the relationship between them and generalized arterial disease investigated both clinically and morphologically but again without general

agreement

The manifestations of arterial disease in diabetes can conveniently be considered in relation to the organs most commonly affected. These are -

(1) the eyes and kidneys
(2) the brain and heart
(3) the lower extremities

I do not propose to discuss the nature of the lesion in diabetic retinopathy of which Ashton (1959) has very recently written a masterly account nor shall I attempt to add anything to Kimmelstiel and Wilson's description of the specific renal lesion which bears their name suffice it to say that these two lesions appear to have much in common both histologically and clinically and when combined with hypertension constitute the most common cause of death from diabetes Outside these organs it is difficult if possible to distinguish the arterial disease of the diabetic from that of the non-diabetic

The Brain and Heart

The clinical manifestations of arterial disease in these organs are commonly cerebral thrombosis and haemorrhage on the one hand and angina of effort coronary thrombosis and heart failure on the other In my experience cerebro-vascular accidents apart from those associated with diabetic nephropathy are related more closely to the age of the patient than to the severity or duration of the diabetes this is not to say that at the same age such accidents are not more common in the diabetic To put it in another way there is little evidence that in this situation diabetes alone produces a specific arterial lesion liable to cause cerebral thrombosis or haemorrhage

When we consider the heart the evidence in support of the aetiological role of diabetes is more suggestive It is generally agreed that the greater incidence of coronary thrombosis in males is less evident female diabetics being more prone to coronary thrombosis than non-diabetic women of comparable age The earlier incidence of angina and coronary thrombosis in diabetics is again often quoted as evidence of a causal relationship but I have been impressed by the fact that in many of these young cases not only is there a family history of both diabetes and coronary artery disease but also that in many the diabetes is of comparatively short duration being first recognised as a result of a routine urine examination at the time of admission to hospital on account of the cardiac condition

The high incidence of obesity in mild and often hyper-

tensive diabetic women may again be a factor of some importance in relation to the incidence of coronary artery disease in the cause of which much emphasis is laid these days on disordered fat metabolism

Lower Extremities

From the point of view of treatment lesions in this position have a special importance and I will therefore make no apology for devoting to them the greater part of this paper

There can be no doubt that gangrene of the toes and feet is many times more common in the diabetic than the non-diabetic this fact has been widely accepted as conclusive evidence that diabetes causes occlusive peripheral vascular disease I hope you will not quote me as saying that it does not do so but here again other factors must be taken into consideration It is convenient to classify lesions of the feet in diabetics under four headings - (Oakley 1954)

(1) Septic
(2) Neuropathic
(3) Ischaemic
(4) Combined

During a survey of the incidence of neuropathy in the Diabetic Department at King's College Hospital Martin (1952) was impressed by the high incidence of foot lesions including gangrene In most cases especially those below the age of 60 the blood supply to the feet as judged by colour temperature arterial pulsation and oscillometry was adequate or even good and it was evident that the lesions were not due to occlusive arterial disease The impairment of sensation both superficial and deep and the frequency of Charcot s arthropathy supported the view that these lesions were the result of trauma on a foot desensitised by neuropathy local arterial thrombosis producing areas of terminal gangrene indistinguishable in appearance from those resulting from more generalised ischaemia (Figures 1 and 2) Conservative treatment in such cases gives excellent results and in the absence of deep sepsis surgery is rarely necessary (Figure 3) Once aware of this pitfall in the diagnosis of diabetic gangrene it was found that about ,0 per cent of the lesions seen in our foot clinic were associated with diabetic neuropathy and there was a consequent reduction in operative treatment This does not however account for the higher incidence in diabetics of true ischaemic gangrene In a study of 3 788 diabetics attending our clinic (Oakley Catterall and Martin 1956) 146 were found to have symptoms and signs of peripheral vascular disease These were analysed to determine the relationship



Figure 1



Figure 2

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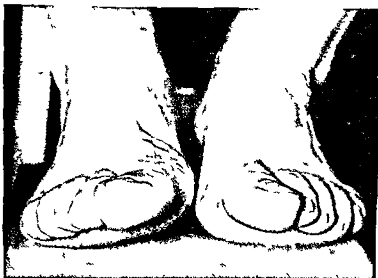


Figure 3

By kind p mi on of the Ed to Annals of the Royal Coll ge of Surg on

between the condition and the age sex and the duration of diabetes

The results are summarised in Tables I II and III from which it will be seen that arterial disease was twice as

Table 1

AGE GROUP	MALES PER 100 DIABETICS	FEMALES PER 100 DIABETICS	RATIO MALE/FEMALE
20-29	-	-	
30-39	-	-	
40-49	2	1	2/1
50-59	4	2	2/1
60-69	11	4	275/1
OVER 70	23	5	46/1

INCIDENCE OF PERIPHERAL OCCLUSI E ARTERIAL DISEASE IN DIABETES WITH RESPECT TO AGE AND SEX

(By k nd permi ion of th Edito B iti h Medical Jou nal)

common in patients of 70 or over as it was in the 60 to 69 age group (Table I), male diabetics were much more commonly affected than females especially in the older age groups (Table II) and the incidence of symptoms and signs of peripheral

Table 2

Age group	Male distribution: Arterial disease	Male distribution: Diabetic population used	Female distribution: Arterial disease	Female distribution: Diabetic population used	Total (arterial disease)	Total (diabetic population)	Incidence in diabetic population
20-29	–	186	–	221	–	407	
30 39	–	222	–	203	–	425	
40 49	4	227	2	226	6	453	13%
50 59	11	280	9	531	20	811	25%
60 69	31	292	28	762	59	1054	56%
over 70	36	159	25	479	61	638	105%
TOTAL	82	1366	64	2422	146	3788	31%
Percentages	56%	36%	44%	64%			

[illegible]

(By kind permission of the Editor British Medical Journal)

arterial disease appears to bear no relationship to the duration of the diabetes the number of patients affected being approximately the same in all groups (Table III)

Table 3

Duration of diabetes in years	Number of patients
Less than 1	20
1-4	26
5-9	29
10-14	25
15-19	26
Over 20	20
TOTAL	146

Incidence of peripheral occlusive arterial disease in diabetics with respect to duration of diabetes

(By kind permission of the Editor British Medical Journal)

From the point of view of treatment ischaemic lesions of the feet in the diabetic (and in our opinion also in the non-diabetic) fall into three main categories

(1) The painful ischaemic foot
(2) Gangrene confined to one or more toes
(3) Gangrene involving the foot proximal to the toes

The first condition which is often associated with intermittent claudication is readily diagnosed from the history of intense burning pain worst at night and unrelieved by vaso dilator drugs The foot is typically pink and cold and although ulceration may occur gangrene is uncommon Treatment consists in keeping the part cool and insuring relief of pain and sleep by means of analgesic and hypnotic drugs of which a combination of physeptone and barbiturates has in our hands given the best results The majority of these cases ultimately require amputation often at their own request but the longer this is postponed the more likely is a painful phantom limb to be a sequela of the operation

Recently as an alternative to below-knee amputation sympathectomy has been carried out on a small number of our cases and we have been impressed in some by the relief of pain which has followed the operation skin temperature and claudication have not been affected

Gangrene confined to one or more toes is best treated by local amputation conservative measures being less satisfactory and no safer on account of the risks attendant upon prolonged confinement to bed or alternatively upon trauma in ambulant cases Figure 4 shows the lower extremities of an elderly woman who was treated conservatively for gangrene of the left big toe After two months in bed she was allowed up knocked her foot against a chair leg and developed a spreading gangrene which necessitat d below-knee amputation About a year later she was readmitted with gangrene of her right big and second toes and rightly insisted on immediate five toe amputation When more than one toe is involved it is often wise to remove all five toes as this procedure carries little if any more risk than the removal of a single toe and at the same time anticipates further and possibly more serious trouble in the remaining digits

When gangrene extends proximally to involve the foot below-knee amputation is the best solution (Silbert 1944) In the past ten years nearly 100 cases have been so treated by Mr Catterall at King s College Hospital and in only one has re-amputation above the knee been necessary there were four post operative deaths The majority of patients manage to walk well after this operation and if as is not infrequently the

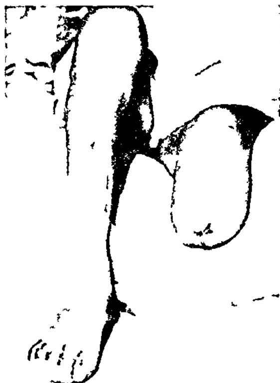


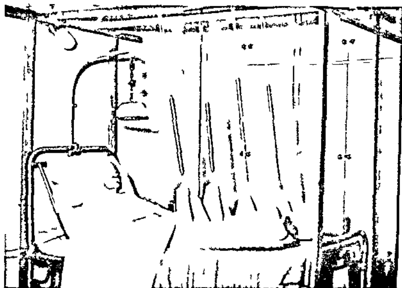
Figure 4

By kind p rmission of the Edito Annal of the Royal College of Surg ons

case the other leg has later to be amputated the preservation of the knees saves the patient from becoming a hopelessly dependant invalid

I have purposely said nothing about arterial surgery in these cases, but although the majority of cases of diabetic gangrene are not suitable for such treatment there are some with relatively high arterial block on one side and an adequate blood supply on the other in whom a bye-pass graft may give a good result

No matter what form of treatment is adopted immobilisation of the diabetic with ischaemic foot lesions carries with it a grave risk of pressure gangrene of one or both heels To prevent this we have devised a method of spring suspension of the lower limbs which when properly carried out has found favour both with the patients and the nursing staff (Figure 5)



F gu e 5

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In conclusion of this brief survey of arterial disease and diabetes I would like to stress that the relationship between these conditions is not so simple and direct as it is g nerally supposed to be and that in re pect of treatment at any rate arterial disease is essentially the same in the diabetic as it is in the non-diabetic subject although the former may require it more frequently and at a rather earlier age

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Treatment of Peripheral Vascular Disease
1—Medical

J F GOODWIN

During the last ten years better understanding of the normal and pathological physiology of the peripheral vascular system and improved surgical techniques for the treatment of vascular obstruction have revealed striking limitations in medical methods of treatment which in many cases is of restricted benefit and strictly palliative nature Nevertheless medical treatment has a part to play and its aims may be defined as follows -

1 General (a) The management of cardiovascular and other associated diseases such as diabetes mellitus
(b) The prevention of further peripheral vascular disease such as arterial embolism

2 Local (a) Improvement of blood flow to ischaemic tissue by vasodilatation
(b) Treatment of ischaemic skin and tissue
(c) Treatment of intermittent claudication and Raynaud's disorder
(d) Treatment of ischaemic rest pain

It is of the greatest importance constantly to bear in mind that peripheral vascular disease is often a manifestation of a generalised vascular disorder This is especially true of atherosclerosis obliterans which also affects the coronary arteries in around 40 per cent of patients with peripheral arterial disease (McDonald 1953) Definitive surgical treatment for peripheral disease is thus often impracticable because of severe heart disease and the treatment of such patients must depend upon medical methods with the exception of amputation for gangrene or intolerable ischaemic pain

It is also of great importance to realise the value of definitive surgical treatment such as arterial grafting and to present the patient who can be helped in this way to the surgeon in good general condition before the disease has advanced too far

The most important peripheral vascular diseases are those

which involve arteries, and may be listed as follows

1 Raynaud s Disorder

Primary

Secondary - such as Thrombo-angiitis obliterans
Diffuse sclerosis (Scleroderma)
Disseminated lupus erythematosus
Associated with cold agglutinins
Associated with embolism
A sociated with rheumatoid arthritis

(In the secondary type of Raynaud s disorder digital artery thrombosis is often a feature)

2 theroscleroeis obliterans

3 Arterial embolism

4 pecific arteritis Thrombo-angiitis obliterans
Diffuse sclerosis
Giant cell arteritis
Polyarteritis nodosa

Treatment is based upon attempts to increase blood flow to ischaemic limbs and it must be admitted that medical methods are inferior to surgical no medical manoeuvre or drug being capable of producing the sustained increase in skin blood flow localised to the affected limb which can result from a good sympathectomy

Vasodilatation may be induced medically by heating the body (Lewis and Pickering 1931) the warm d blood from the limb reaching the heat regulating centre and inducing vasodilatation by a central and also local action The patient with an ischaemic limb should be nursed in a warm environment if possible at 80 - 87°F (27 - 30°C) The ischaemic limb should be protected from injury by a cradle but should be expo ed to the air On no account should any local heat be applied since the d vitalised skin easily becomes burnt and any increase in local blood flow which has been produced will be insufficient to meet the demands created by the external heat Heat may be applied to the trunk or to the normal limbs by means of heat cradles blankets or a special heating arm or sleeve and can produce an increase in skin blood flow even in the presence of severe ischaemic disease (Figure 1)

aravertebral procaine block has a transient action and cannot be repeated indefinitely

Ethyl alcohol in the form of whiskey or brandy is a simple and useful vasodilator and has the additional advantage of sedative and euphoric effects It is particularly useful given at night to elderly patients but of course has the disadvantage of habituation if given regularly for a long period Alcohol possibly enhances the effect of reflex heating

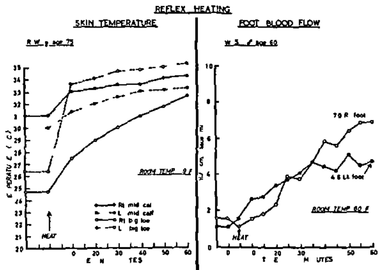


Figure 1 Increase in skin blood flow to the lower extremity after refl x heating measured by sk n temperatu e (left) and by venous occlusion pl thysmog aphy of the foot (right) in two patients with occlusive peripheral arterial disease
In each case an increase in skin flow r sults f om reflex heating even in the p esence of organ c arterial disease

Vasodilating drugs are of doubtful effectiveness because of a therapeutic paradox The ideal vasodilator is one which produces selective and sustained vasodilatation in the affected part without lowering blood pressure producing considerable side effects, tachyphylaxis or tolerance It follows that the more effective the vasodilator the more widespread and marked the effect and the greater the hypotensive action Generalised vasodilation leading to appreciable hypotension defeats its own object since the limb perfusion pressure becomes reduced and blood flow may actually fall It is not possible to restrict the action of the drug to the affected limb as with sympathectomy and hence the paradox that the greater the degree of vasodilatation the less may be the value to the ischaemic limb However vasodilators do have some effect because moderate vasodilatation is insufficient to reduce the blood pressure significantly and also because of a selective action upon digital vessels

The most effective vasodilators are those which act by reversal of adrenergic vasoconstriction by ganglion blockade or by adrenolytic or sympatholytic effects Some of them also have a local action on the blood vessel wall The terms adrenergic blocking adrenolytic and sympatholytic are often

used synonymously Although a sympatholytic drug must by strict definition also by adrenolytic the reverse is not necessarily true Certain drugs such as dibenylene could be considered as purely adrenolytic but in practice the separation of adrenergic blocking (adrenolytic) agents into sympatholytic and adrenolytic groups is now considered largely artificial

TABLE

The commoner vasodilating drugs are listed below -

Drug	Effect on blood pressure	Action	Side Effects	Tolerance
Hexamethonium Pentolinium Mecamylamine Pempidine		(Ganglion (blockade	Appreciable due to parasympathetic inhibition	+
Imidazoline (Priscol)		Sympatholytic Local Mainly on small vessels	Variable Dizziness Palpitations Gooseflesh	0
Phentolamine (Rogitine)		"	"	0
Dibenylene		Sympatholytic	Variable	0
Azepetane phosphate		Sympatholytic Local Mainly on small vessels	Mild	?
Vasculit	0	Sympatholytic	?	?
β Pyridil carbinol (Ronicol)	0	Local	Flushing	?

The ganglion blocking agents are clearly unsuitable for routine use because of their hypotensive action and unpleasant side effects although a considerable increase in limb blood flow can be produced by an injection of hexamethonium (Hamilton et al 1954)

In my experience the most effective drugs for use in peripheral vascular disease are Imidazoline (Priscol) (Goodwin and Kaplan 1950) Phentolamine and Dibenylene (Wertheimer et al 1954) The former can produce appreciable vasodilatation in the skin of the ischaemic limb when given by injection, especially if this is intra-arterial (Lynn 1950 Edwards et al 1952 Prandoni and Moser 1954) although the action may be disappointingly transient (Catchpole and Jepson 1954) Prolonged therapy by the oral route may achieve some limited success as is shown in Figures 2 and 3 although this objective

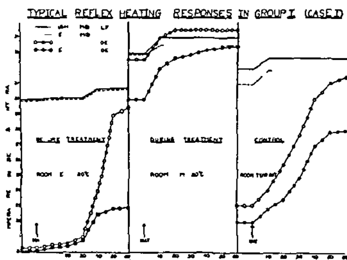
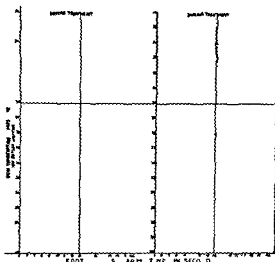


Figure 2 Effect of treatment with oral Imidazoline on skin temperature in a patient with occlusive peripheral arterial disease Before treatment the resting skin tempe atures of both great toes are low and the left increases only slightly after reflex heating During treatment the resting temperatures are considerably higher but after treatment has been discontinued (control) the resting temperatures approximate to the p e treatment level although the response of the left great toe resembles that during treatm nt The results indicate that Imidazoline can have a su tained effect when given orally
(Male aged 61 Durat on of treatment 9 weeks Subjective improvement) (By kind pe mission of the Editor British Medical Journal)

evidence of vasodilatation is not always accompanied by sustained clinical improvement presumably due to the progressive nature of the occlusive disease It must also be remembered that clinical improvement may occur without any specific therapy at all owing to the opening up of collateral vessels so that the assessment of vasodilating drugs by clinical observation alone over a long period is fraught with difficulty



Figu e 3 The effect of oral Imidazolin on c rculation rate to the lower limb and on skin temperature Each dot represents one limb During treatment the circulation t me has hortened and the skin temperature r sen in the majority of limbs show ng an im provement in circulation
(Duration of treatment 1 12 week C rculat on to the low r l mb (foot minus hand t me) mea ured by th fluorescein m thod of MacGregor and Wayne (1951) (By kind perm s ion of the Editor British Med cal Journal)

Occasionally patients find the side effects of sympatholytic drugs highly unpleasant and become very conscious of palpitation dizziness headache and gooseflesh It is well therefore to start with a small dose and then work up to a larger maintenance dose Thus the initial dose of Imidazoline should be 25 mgm thrice daily and the maximum 100 mgm four times daily Sometimes patients will tolerate one of these drugs but not another so that it is worth trying all members of the group in turn Patients with a history of peptic ulcer should be given alkalis at the same time since the adrenergic blockade tends to increase gastric excretion and may induce vomiting Dibenylene tends to produce less gastric effects than Imidazoline and is therefore to be preferred when gastric complications are feared

One or more sympatholytic drugs may be used in combination though there is no certain evidence that they exert a synergistic action

The doses of the drugs mentioned are given below -

Drug	Initial oral dose	Maximum oral dose
Imidazoline	25 mgm three times daily	100 mgm four times daily
Phentolamine	25 mgm three times daily	100 mgm four times daily
Dibenylene	10 mgm twice daily	60 mgm twice daily
Azopetane phosphate	25 mgm three times daily	100 mgm three times daily

Care should be taken when Imidazoline is given by injection in high dosage to patients with coronary artery disease since an undue fall in blood pressure can occasionally occur and the adrenergic blocking action may have an adverse action on coronary blood flow Intravenous and intra-arterial injections should be given slowly and well diluted and the initial dose should not be more than 25 mgm Intramuscular injections of up to 75 mgm may be given 3 to 4 times a day, and supplemented by oral therapy if well tolerated The action of all these drugs is enhanced if the patient is kept in a warm environment Their duration of action is from 4 - 6 hours with the exception of Dibenylene which acts for up to 12 hours

Vasculit" is a newer adrenergic blocking agent which effectively reverses the vasoconstrictive effect of adrenalin It is a derivative of phenylephrine, and when given by injection produces appreciable vasodilation in the limb vessels without appreciable hypotensive effect or change in heart rate (Duff 1959)

β pyridil carbinol (Ronicol) is the alcohol corresponding to nicotonic acid, has a purely local action on blood vessels It is of little clinical value but may be tried in combination with a sympatholytic drug

The action of all vasodilators is maximal in the presence of reversible vasoconstriction as in primary Raynaud s disorder and often disappointing when organic arterial occlusion is present Prolonged treatment with the maximum tolerated dosage should be attempted for half-hearted regimes are doomed to failure Adrenergic blocking agents may be of some value after sympathectomy when nerve endings have become unduly sensitive to circulating adrenalin

TREATMENT OF SPECIFIC DISORDERS

1 PRIMARY RAYNAUD'S DISORDER

The patient should be instructed to avoid as far as possible local cold stimuli and should wear warm gloves in the winter Smoking should be curtailed and attention should be

paid to other possible precipitating causes such as the use of vibrating tools Cervical ribs and shoulder girdle syndromes should be looked for and occasionally exercises designed to elevate the shoulder girdle may help The carrying of heavy weights for prolonged periods or sleeping with the arm above the head should be avoided Vasodilator drugs should always be given a trial and at times may be successful

2 SECONDARY RAYNAUD'S DISORDER

Frequently digital arterial disease is present which often leads to thrombosis The measures already outlined for promoting vasodilatation should be employed and in addition the generalized vascular and connective tissue disorder requires energetic treatment

Thrombo angiitis obliterans Smoking must be denied the patient absolutely After acute episodes of vascular occlusion anti-coagulants may help but are likely to be of limited value only because thrombosis is secondary to arterial inflammation which is basically uninfluenced by any specific medical measure except abstinence from tobacco Long term anti-coagulants may be worthy of trial and vasodilator drugs should be given Steroids do not appear to have any marked beneficial effect but may also be tried in acute cases The majority of patients come to sympathectomy Of 14 cases at Hammersmith Hospital of proved or suspected thrombo-angiitis with arterial involvement 13 required sympathectomy and 3 came to amputation of digits or of a limb In only 1 patient was the disorder apparently arrested after medical treatment alone

Since the disease occasionally involves the coronary and visceral arteries (Allen et al 1946) a careful appraisal of the whole vascular system is required in planning treatment (Figure 4) Care of the ischaemic extremities is of paramount importance and the same principles apply as in the treatment of ischaemia due to arteriosclerosis obliterans which will be discussed later

Diffuse sclerosis (Scleroderma) The secondary Raynaud s phenomenon in this disorder is very commonly associated with digital thrombosis and a regime of vasodilatation anti-coagulants and steroids drugs may achieve some benefit In a personal case of a woman with valvular heart disease digital thrombosis and Raynaud s phenomenon (probably due to scleroderma) treatment with anti-coagulant therapy and vasodilator drugs for six months with prednisolone for two months was followed by improvement in the blood supply to the fingers In many cases of severe scleroderma the visceral and cutaneous manifestations overshadow those of peripheral vascular disease but treatment with intravenous procaine and para-amino benzoic acid has been

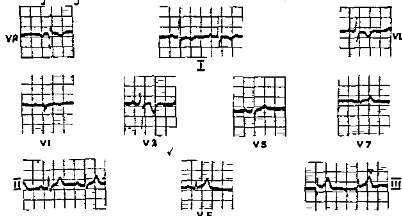


Figure 4 Cardiogram of male patient aged 36 years with thrombo angiitis obliterans and ischaemic cardiac pain The graph shows *inversion of T wave in I V3 and VL indicating anterior and lateral* subepica dial infarction due either to thrombo angiitis obliterans or to associated coronary atherosclerosis obliterans

most unimpressive, and unfortunately steroids do not often help The synthetic chelating agent ethylene diamine tetra-acetic acid has been suggested for removing calcium in cases of scleroderma with calcinosis (Winsor 1959)

Disseminated lupus erythematosis Raynaud s phenomenon is seldom an important feature of this disease and digital thrombosis is uncommon Treatment usually with steroids is therefore concentrated on the systemic disease and vasodilators are used when required

Raynaud s phenomenon has been described in association with haemolytic anaemia and a high serum titre of cold agglutinins and cold haemolysins (Ferriman et al 1951) The Raynaud s phenomenon is most probably due to obstruction of the peripheral circulation by autohaemoagglutination in vivo Since agglutination is precipitated by cold it is vital that when the condition is suspected the patient be placed in a very warm environment if cold agglutinins are found in the serum The value of steroids is uncertain in such cases

Raynaud s phenomenon may sometimes result from digital occlusion due to small emboli from a thrombus or embolus in a proximal limb artery The treatment is likely to be mainly surgical but the cause must be investigated ard prelimirary medical treatment carried out along the usual lines

In all cases of secordary Raynaud s disorder manifestations of systemic disease such as heart failure and anaemia will

exacerbate the condition and must be diligently treated

ATHEROSCLEROSIS OBLITERANS

Frequently occlusive arterial disease of the extremities is accompanied by disease of the coronary or cerebral arteries and by hypertension The medical management of such patients with peripheral disease must include careful appraisal and control of generalised disease and particularly of diabetes mellitus if present Tobacco should be restricted but alcohol allowed in moderation Insufficient is yet known about satisfactory ways of controlling the progression of atherosclerosis but a low calorie diet is advisable when the patient is overweight and if there is a strong family history and high blood cholesterol a diet low in animal fat supplemented by vegetable fat such as corn or maize oil may be advocated The position of long term anticoagulant therapy for atherosclerosis obliterans involving peripheral arteries has not been defined but such therapy should be seriously considered in the young patient with a strong family history

The patient with occlusive disease usually suffers from manifestations of skin ischaemia (numbness paraesthesiae coldness and ultimately gangrene) of nerve ischaemia (rest pain) and of muscle ischaemia on effort (intermittent claudication)

All these disabilities could be relieved by increasing sufficiently the blood supply to the limb The only really effective way of achieving this in the present state of knowledge is an effective arterial grafting procedure Medical measures are relatively inefficient for all methods produce a significant vasodilatation only in the skin blood vessels Nevertheless some improvement can be obtained by energetic medical treatment aimed at causing vasodilatation by the methods and drugs already described

Care of ischaemic skin prevention and treatment of gangrene

Much can be done to minimise the effects of ischaemia and delay the onset of necrosis by careful management Trauma should be carefully avoided and any local abrasion should be covered and shielded from infection which may lead to gangrene and further arterial occlusion Toe nails should be cut squarely and the help of a skilled chiropodist is often of great value The feet should be kept warm clean and dry and after washing a talc dusting powder should be used in the socks Fungus infection should be diligently treated as this may lead to breach of the skin infection and possibly further arterial disease Castellani s carbol fuchsin paint or undecylenic acid ointment or powder should be used

On no account should direct heat ever be placed on or close to an ischaemic limb and patients must be instructed forcibly on this matter

When gangrene has occurred the patient should be confined to bed on full vasodilator therapy If the gangrene is dry and uninfected clean separation may occur, or digital amputation may be required When infection is present local crusts or sloughs should be gently soaked off in boric acid or potassium permanganate (1 10 000), or Eusol packs applied Prolonged application of wet dressings should be avoided as they tend to macerate viable tissue Antibiotics may be applied locally avoiding penicillin and sulphonamide because of the risk of sensitisation Bacitracin solution (1,000 units per ml) is useful for sensitive gram positive organisms and certain penicillin resistant organisms for it is not inhibited by penicillinase Neomycin ointment or solution is of value and is effective against a wide range of gram positive and negative organisms and sometimes against pyocyaneus and proteus infections Polymyxin ointment should be used against the former In many cases however it is preferable to give antibiotics parenterally although they may have difficulty in reaching ischaemic tissue via the blood stream Necrotic tissue can be removed by the use of wet dressings of streptokinase (100 000 units and strepto-dornase (25,000 units) in 20 ml of saline or by the use of a jelly containing the enzymes which dissolve necrotic tissue (Hines and Gifford 1957)

In old persons especially an adequate diet with vitamin supplements, and control of anaemia, heart failure or diabetes is of paramount importance

Ischaemic rest pain This intolerable pain which prevents sleep is extremely difficult to relieve and is usually an indication for amputation It may be alleviated slightly by opium alkaloids (papaveretum) by diamorphine and by synthetic morphine-like substances such as Levorphanol tartrate (2 mgm every 6 hours) Pethidine is of little value but the so called "tranquillizers such as methyl pentynol carbonate or meprobamate (200-400 mgm 3 or 4 times daily) may be of help In any but the elderly patient with limited prognosis the use of narcotics for any length of time is highly undesirable because of the risk of addiction

PERIPHERAL ARTERIAL EMBOLISM

Adequate treatment depends upon recognition of the causes and prognosis The former are listed below

1 Previous thrombosis in pulmonary veins left atrium or left ventricle associated with mitral stenosis or

cardiac infarction and heart failure (Drew Miller et al 1952)

2 Arrhythmia (usually atrial fibrillation)

3 Intracardiac obstruction or infection as in mitral stenosis or infective endocarditis

4 Paradoxical embolism from peripheral venous thrombosis through a patent foramen ovale

Intracardiac thrombosis and subsequent embolism are most likely to occur when both obstruction to flow and arrhythmia are associated and this accounts for the frequency in mitral valve disease Emboli are frequently multiple and have a tendency to recur once a patient has begun to produce emboli he tends to continue to do so (Daley et al 1951) Peripheral emboli are not infrequently silent especially in mitral valve disease Jacobs (1959) examined 269 patients with mitral stenosis and 300 controls and found evidence of recent emboli in 27 per cent of the mitral patients with atrial fibrillation 4 per cent of those with sinus rhythm and 0 6 per cent of the controls When serious embolism occurs however the prognosis is gloomy Martin (1959) reported that of 38 patients admitted to hospital 18 died and 5 required amputation of a limb Fifteen were discharged but only 3 with apparently normal peripheral circulation The high mortality was ascribed to heart disease pulmonary embolism and recurrent systemic embolism

Treatment of established embolism is clearly highly satisfactory whatever medical or surgical means is employed Attention must therefore be focussed both upon prevention of intracardiac thrombosis with subsequent embolism and upon secondary embolism from the original embolus which tends to break up when arrested at an arterial bifurcation and shower daughter emboli into smaller distal vessels This complication undoubtedly often contributes to the failure of embolectomy (Martin 1959)

It is probable that in mitral stenosis when the patient starts to fibrillate thrombosis occurs rapidly in the atrium and the thrombus is either discharged or organised in situ within a few hours If effective anti coagulation could be started at the onset of atrial fibrillation embolism would be discouraged The use of long term anti-coagulants has been claimed to reduce the incidence of embolism in rheumatic heart disease by Wood and Conn (1954) and by Irving Wright and his colleagues (McDevitt et al 1958) as shown below

No of pts	Anti-coagulant therapy	Total pt months	No of pts with recurrent embolism	No of thrombo-embolic episodes
51	0	1747	43	197
	+	1515	20	55

(Modified from McDevitt et al 1958)

These figures are not wholly reliable however for the control group was retrospective and not selected at random or observed concurrently with the anti-coagulant group Nevertheless there is much to suggest that anti-coagulants do significantly reduce the incidence of emboli

Embolism is even more strikingly reduced by mitral valvotomy (Belcher and Somerville 1955) In my own experience of 259 patients who came to valvotomy, 59 had 1 or more emboli previously but only 6 had an embolism in the period from 6 months to 7 years after operation and multiple emboli never occurred

Amputation of the left atrial appendage alone will protect against further embolism in no more than 50 per cent of cases but might possibly be considered if valvotomy is impracticable After successful operation anti-coagulants may be gradually discontinued, but should never be stopped suddenly for this may precipitate thrombosis After reversion of fibrillation to sinus rhythm embolism is even less likely to occur Reversion may occur spontaneously after operation or may be induced with quinidine under anti-coagulant cover but reversion is often not sustained and quinidine may be dangerous even when given in the usual therapeutic dosage

The effects of embolism, especially repeated embolism can be so devastating and the results of treatment so unsatisfactory in mitral valve disease that an aggressive attitude towards prevention is indicated on the part of the physician Therefore in patients who have recently developed atrial fibrillation due to tight mitral stenosis anti-coagulant therapy should be started and mitral valvotomy carried out as soon as possible But thrombus may be detached from the left atrium at valvotomy especially in patients with recent atrial fibrillation in whom the thrombus may be soft and pliable It has been claimed that this hazard may be reduced by covering the operation with anti-coagulant drugs of the coumarin series (Storm and Hansen 1955) Personal experience suggests that this may indeed be so and the preliminary results in a series of patients operated upon by my colleague Mr W P Cleland and his associates, are shown below

Mitral Valvotomy

Total cases (all with atrial fibrillation) = 106

No anti-coagulant cover (No of patients)	Left atrial thrombus	Operative Embolism
62	14 (22%)	5 (3 fatal) (8%)
Anti-coagulant cover		
44	4 (9%) Prothrombin time 14 secs immediately before valvotomy	1 (fatal) (2 3%) Prothrombin time 15 secs

Anti-coagulant cover was provided by Phenindione which was usually started 10-15 days prior to operation Prothrombin times were kept in the therapeutic range whenever possible and it is of interest that in the 2 patients in the anti-coagulant group who had an operative embolism and fresh thrombus in the atrium respectively the prothrombin time was insufficiently prolonged for effective action in preventing new thrombus formation Three patients had haemothoraces which did not cause death in any and might have been attributable to the thoracotomy rather than the anti-coagulant

These results are merely provisional it remains to be seen whether further study of more patients will support the trend towards protection from operative embolism afforded by anti-coagulants

Recurrent embolism will continue to remain a problem however until more is known of the underlying physical and biochemical causes of intracardiac and intravascular thrombosis

TREATMENT OF ACUTE ARTERIAL EMBOLISM

Pain should be controlled with papaveretum or pethidine The limb should be exposed to a high ambient temperature and the trunk heated One or two ounces of brandy by mouth should be given and anti-coagulation started with 100 mgm heparin intravenously and 100 mgm of phenindione by mouth

Rapid atrial fibrillation should be controlled with digitalis using intravenous digoxin if the need is urgent and the patient is not already receiving digitalis No attempt should be made to revert the fibrillation to sinus rhythm with quinidine at this stage

Intramuscular injections of Imidazoline should be given every 3 hours and if an artery proximal to the embolus is easily accessible an intra-arterial injection may be given Great care must be taken to compress the artery after puncture if the patient has been heparinized lest a large haematoma

result Congestive heart failure if present should be treated in the usual way The vascular surgeon should see the patient in consultation on admission to hospital and if signs of limb ischaemia persist after 1 or 2 hours embolectomy should be undertaken provided the patient s general condition permits it

The chances of saving the limb depend upon several factors notably the interval between the occurrence of the embolism and treatment the size of the artery involved and the amount of secondary embolism in the limb As would be expected the limb survival is inversely related to the size of the artery obstructed (Jacobs 1959)

Anti-coagulant therapy must be continued and should on no account be stopped suddenly a few days after the embolism

In patients with mitral valve disease valvotomy should be considered as soon as cardiac function is satisfactory and the limb out of danger Naturally all patients will not have stenosed mitral valves suitable for valvotomy but the majority will for serious or repeated embolism is rare in dominant or lone mitral incompetence

CONCLUSION

In many forms of peripheral arterial disease definitive treatment lies in the hands of the surgeon The physician s part should lie in general management prevention of further arterial disease and supportive treatment of ischaemic limbs

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Treatment of Peripheral Vascular Disease 2—Surgical

G W TAYLOR

Occlusion of the large limb arteries is most frequently caused by atherosclerosis and in considering surgical measures in this form of the disease two facts must be kept in mind The first is that the peripheral form of atherosclerosis is a relatively benign disease Of 408 patients attending the Vascular Clinic at St Bartholomew s Hospital major amputation became necessary in only 44 (10 per cent) over a period of observation ranging from 4 to 10 years The second fact is that surgical treatment does not influence the basic pathological disturbances in occlusive arterial disease and this form of therapy is therefore best regarded as a palliative measure useful when certain complications occur Aneurysm formation and arterial stenosis or occlusion are the complications responsible for the major symptoms of atherosclerosis of the limb arteries

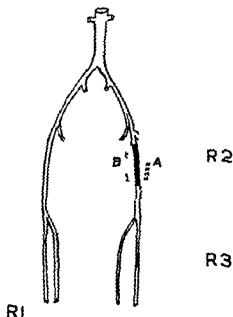
<u>Aneurysm formation</u>

Peripheral aneurysms occur most frequently in the femoral or popliteal arteries and multiple lesions are not uncommon Severe symptoms from the physical presence of an aneurysm in these sites are rare but the risk of rupture or of total thrombosis within the sac is sufficiently great to warrant treatment whenever the diagnosis is made Current surgical treatment is directed toward excision of the lesion and restoration of normal blood flow This may be accomplished occasionally by excision of the aneurysm and end to end anastomosis of the proximal and distal arterial segments but more usually arterial grafting is necessary to restore vascular continuity The uninvolved arterial tree is usually of good calibre and patency in patients with peripheral aneurysm and the results of grafting are very satisfactory (Crawford et al 1959)

<u>Arterial stenosis or occlusion</u>

Diminished blood flow distal to a major arterial occlusion may be responsible for intermittent claudication or pain at rest indicative of nutritional disturbance in the limb The second symptom is the more serious and gives warning that the

safety of the limb is endangered Sympathectomy or a direct operative attack on the diseased main vessel are the only surgical measures capable of favourably influencing blood flow distal to an oc lusion The therapeutic problem is to decide *for which symptom and in which patients these methods should be* used Under steady inflow conditions the blood flow in a normal limb is dependent largely on the peripheral resistance offered by the capillary beds of the skin and the muscle masses (Figure 1 R1) With main artery occlusion a further impedence (Figure 1 R2) is superimposed on the existing peripheral resistance The result will be a reduced flow in the tissues distal to the block and the magnitude of the reduction will depend ultimately on the degree of development of the collateral *circulation In general a single block will produce symptoms* of claudication only while multiple occlusions with additional impedence (Figure 1 R3) are associated with nutritional



Figur 1 Di g am of po bl mp d nc s to blood flow off r d by s gmental occlus ons in the m in stem art ies

disturbance and gangrene Sympathectomy exerts its chief and *immediate effect by diminishing the vasoconstrictor tone of the* small arterioles supplying the skin The clinical benefits of sympathectomy are therefore largely confined to an improvement

in skin flow and this can only occur if the collateral circulation around the more proximal pathological impedences permit sufficient flow to fill the denervated and dilated cutaneous vascular bed Whether or not this improvement in skin blood supply takes place depends not on an abolition of abnormal vasoconstriction in the diseased limb but solely on the degree of main vessel occlusion and the state of development of the existing collateral circulation Sympathectomy is most effective in patients in whom there is cutaneous ischaemia and yet whose existing collateral circulation is adequate to allow improved flow through the denervated skin This is the clinical stage of early nutritional impairment and is characterised by well developed postural colour changes coldness of the foot and slight rest pain In this context other minor sensory disturbances such as transient numbness and paraesthesia are included in the category of rest pain Table I compares the results of

TABLE I

Patients with Slight Nutritional Change

	No	Improved	Unchanged	Worse
Sympathectomy	82	66 (80%)	4 (5%)	12 (15%)
No operation	45	22 (49%)	19 (42*)	4 (9%)

sympathectomy at this clinical stage with a similar group of unoperated patients There is a significant increase in the number of patients improved by sympathectomy although this operation did not lessen the proportion of patients who deteriorated in later years Sympathectomy done before this clinical stage of the disease is unnecessary and is of no benefit in the more advanced stages of vascular impairment characterised by severe rest pain with impending or actual gangrene This latter state is always associated with extensive main artery occlusion and a collateral circulation inadequate to take advantage of the decreased peripheral resistance obtained by sympathectomy Sympathetic denervation will never save a limb once the question of major amputation is under consideration

From the foregoing it will be clear that sympathectomy is unlikely to influence intermittent claudication in that the large blood flow demands of the working muscle will not be met by the small overall increase in flow through the collateral bed obtained by diminishing the cutaneous peripheral resistance

Table II compares the results of sympathectomy in patients with

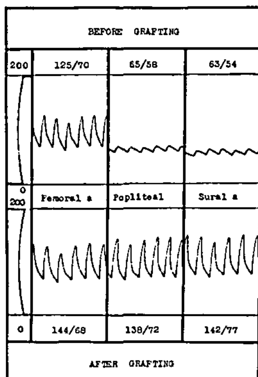
TABLE II
Patients with Claudication

	No	Improved	Unchanged	Worse
Sympathectomy	65	16 (24%)	41 (64%)	8 (12%)
No operation	84	21 (25%)	57 (68%)	6 (7%)

claudication with a similar group of unoperated patients Both groups were followed over a period ranging from 4 to 10 years and it can be seen that there is little difference in outcome Intermittent claudication can only surely be relieved by a spontaneous major increase in the collateral circulation or by some form of direct arterial surgery Walder (1958) has pointed out that a high perfusion pressure is needed to ensure adequate flow through the exercising calf muscle Both pressure and flow are reduced in the main artery distal to an occlusion and direct arterial surgery is the only effective method of restoring normal pressure and flow relationships (Figure 2) The main indication for sympathectomy in occlusive vascular disease then is at the stage of early nutritional disturbance The immediate effects of operation at this stage are good and the resulting slight increase in blood flow through the collateral bed may in the course of time stimulate further development of these important vessels

Direct arterial surgery

The realisation that peripheral occlusive disease affects mainly the large stem arteries and that the process is commonly segmental in nature has led to the development of direct surgical attack on the diseased vessels Thrombo-endarterectomy and arterial grafting are the most generally useful methods although occasionally a short segment of occlusion may be reset
occlusion may be resected with direct repair of the divided vessel Thrombo-endarterectomy is most successful in relieving relatively short blocks in large diameter vessels and is the operation of choice in disease confined to the aorta-iliac segment Arterial grafts must be used when the occlusive disease involves long lengths of the narrower femoro-popliteal regions of the peripheral arterial tree and the by-pass method of insertion has become established as the technique of choice The ideal material for arterial grafts has yet to be found The use of autogenous vein (usually the long saphenous) has



F gu e 2 Resting pressures in the Femo al Popliteal and Sural arteries in a patient with Femoral artery occlusion and severe claudication Normal pre sure is restored to the distal vessels afte by pass grafting

obvious theoretical advantages and has yielded good results (Linton 1959 Dale and Mavor 1959) but in advanced ischaemic disease the available veins are often diseased or too short for the purpose Preserved arterial homografts have been used extensively but are difficult to obtain troublesome to process and may be prone to degeneration many months after implantation into the limb (Szilagyi et al 1957 Hoye and Warren, 1956) The recent trend in arterial replacement is toward the use of plastic prostheses and while a large variety of synthetic tubes have been shown to function adequately in the aorta-iliac segment it is as yet too early to assess their use in the narrower femoral and popliteal arteries Currently tubes of knitted crimped Dacron (terylene) (Crawford De Bakey and Cooley, 1958) or woven teflon (Verendino Girvin and Thomas 1958) are popular and have a high rate of initial success The long term results remain to be seen and must await reports of careful and accurate follow-up studies with detailed analysis

of the state of the arterial tree at the time of grafting The indications for direct arterial surgery must necessarily be influenced by such factors as the mortality rate for these operations and the degree of success in maintaining arterial patency over long periods of time Table III gives an indication

TABLE III

	Mortality Rate
Aorta-iliac	5% (36% - 3%)
Femoro-popliteal	2% (11% - 1 4%)

of the mortality rate of direct arterial surgery in the proximal and distal segments of the arterial tree The figures in parenthesis give the highest and lowest mortality range in published series As yet no adequate long term reports of the results of grafting in the peripheral vessels have been published I am however indebted to Professor C G Rob for Table IV which shows his results obtained in 400 patients

TABLE IV

Results in 400 Patients followed for 1½ years or longer (Prof C Rob)

Operation	No of Patients	Dead	Thrombosed	Patent
Direct Suture	20	2	2	16 (80%)
Thrombo-endarterectomy	97	3	8	86 (88 7%)
Autogenous Vein	29	2	14	13 (44 7%)
Homologous Artery	206	12	53	141 (68 4%)
Plastic Prosthesis	48	8	10	30 (62 5%)

followed for 1½ years or longer In general the long term results in the aorta-iliac segments whatever procedure is used are better than in the smaller distal vessels (Freeman and Nicholson 1959 Wylie 1952) At present it would seem reasonable to expect relatively long term success in 80 per cent of operations on the proximal vessels and in 65 per cent of the more peripheral procedures These results are encouraging but can only be obtained by careful selection of patients and meticulous technique Successful direct arterial surgery is most

often achieved in patients with occlusion limited to one segment of the arterial tree and with good proximal and distal vessels This type of lesion usually produces symptoms of claudication only and is unlikely to threaten the limb as a whole Most patients adjust well to intermittent claudication but in the minority who prove intolerant of this symptom, the method of direct arterial surgery appropriate to their lesion offers the best prospect of relief Arterial surgery can sometimes be of great benefit in severe ischaemia when the safety of the limb is threatened and a proportion of such limbs can be saved from amputation The arterial tree in these circumstances is usually extensively diseased and the prospects of early and late success are correspondingly diminished In a personal series of 34 patients with ischaemia severe enough to warrant major amputation arterial grafting was technically possible in 25 patients Table V gives the results of this trial and it can be seen

TABLE V

34 Patients	
25 By-pass grafts (8 Ilio-popliteal	17 Femoro-popliteal)
4 Early failures	4 amputations
6 Delayed failures (2-9 months)	5 amputations
16 Limbs survive (9 > 1 yr)	

Results of direct arterial surgery in ischaemia severe enough to warrant major amputation

that about half the limbs originally at risk have been salvaged The later results in this series remain to be seen but in these elderly patients the preservation of a limb for what may be a comparatively large proportion of their remaining life seems worthwhile

Two further surgical procedures remain to be considered Tenotomy of the tendo Achillis is a minor procedure which can produce striking relief in elderly patients afflicted with crippling calf claudication Finally amputation should not be delayed in severe ischaemia resistant to other forms of treatment Ischaemic pain unduly prolonged can destroy a patient physically and can imprint so strong a mental stimulus that even amputation will fail to bring relief

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DISCUSSION

CHAIRMAN: I would like to begin by thanking the speakers for keeping up to time and now we have twenty minutes left for the discussion and I would like to start it by asking two questions The first is I wonder if anyone has any experience of stopping smoking in thrombo-angiitis obliterans? I think it was Silbert who about 25 years ago suggested that if you did stop the patient smoking that they got no recurrences and I suppose I have had about half-a-dozen patients in the last twenty years with thrombo-angiitis in whom I have stopped them smoking and I have not seen an extension of the disease in any of those patients I wonder if other people have experienced this rather uncommon condition? Now the second question I would like to ask is this is there any evidence about the place of anticoagulants in the treatment of peripheral arterial disease? There are two particular kinds of disease in which one might suspect that it might be useful There is the acute Raynaud which Lewis and I showed a long time ago was due to thrombi in the palmar arch or the plantar arch I have had one patient in the last ten years with that condition treated by heparin from the start who made an unusually good recovery but of course that really is not evidence And the second is, is there any evidence that if the s rgeon has given you a new artery for old either by putting in a bit of the tail of your shirt or a pig s artery or something that you are more likely to remain with your arteries patent if you are treated with anticoagulants than if you are not?

MR TAYLOR: I can answer your second question Sir The answer is that you are more likely to remain with a patent graft on anticoagulation than not

CHAIRMAN: Has that been done with a controlled trial?

MR TAYLOR: Professor Rob has done it and I do not carry his figures in my head but he tells me that the conclusions are quite definite

CHAIRMAN: How long do you keep it up?

MR. TAYLOR: Indefinitely

DR GOODWIN: In only one of my fourteen patients with thrombo-angiitis in whom the condition did not require surgery was the condition apparently arrested by a sensible physician who really did stop smoking

CHAIRMAN: Did the others progress because they smoked or in association with smoking?

DR GOODWIN: No not necessarily

CHAIRMAN: I see they were so bad when you got them

DR GOODWIN: No they were not all extremely bad; some of them were quite mild

CHAIRMAN: But th y required surgery?

DR GOODWIN: They required some form of surgery at some time over a long period a period of 5 years to 10 year

CHAIRMAN: That sounds as though the dis ase progressed?

DR GOODWIN: I think it probably did

CHAIRMAN: And did th y smoke or didn t they smok ?

DR GOODWIN: Most of them I think did smoke but most of th m denied it

CHAIRMAN: Ye yes

DR FLETCHER: I didn t quite follow Dr Oakley s slide about the duration of diabetes and the number of patients He had a h ading in his slide with vascular disease Did he mean number or percentage because if it was a numb r pr sumably there are smaller numbers of patients with very long standing diabet s and this would indicate an increa ing percentage pr valence

DR OAKLEY: Th re w re two slides; the second one wa expr sed in cases per hundred of males and f male In th first slide if my memory serves m it is the a tual number of those in that age group today and th numb r of cas s examined was given on the same slide So you can ex lude the qu tion of wheth r w w re g tting a smaller or larg r number of pati nt in that way

DR ROBERTSON: I would like to ask Dr Goodwin if he thinks there is any place for a machine producing p itive and n gative pressure in the treatment of th e pati nts?

DR GOODWIN: I would ay no Sir b cau e I am always v ry worried about me hanical ontraptions put on to potentially or actually i chaemi limbs I don t r ally think it does any good: it might v ry w ll do harm

PRESIDENT: I would like to a k Mr Tayl r who said that many patients acclimatize th m elv quite well to having intermittent claudication is there any harm in going on waiting provid d that th y are willing to put up with their limitation ? Is one doing any harm in waiting befor con id ring surgery for their treatment?

MR TAYLOR: I pr um you m an some form of direct arterial urgery?

PRESIDENT: Yes

MR TAYLOR: Th re may b some harm Th re may be a tage wh n th re is a short block say in your femoral artery whi h could be v ry ea ily dealt with by thrombo- ndarterectomy and if tr atm nt i po tpon d the clot may extend proximally and distally and the condition may g t wor e The diffi ulty of cour e is to decid when that is going to happen Only 10 p r cent of all patient g t into bad trouble and it would m an inv stigating and possibly tr ating a lot of patients unn e - arily The difficulty is to find which pati nt is going to go bad wh n you fir t see him

DR L. GILCHRIST: I hould like to a k Dr Oakley wheth r the actual control of diab tes influ nces the on t of p ripheral vas ular dis ase

DR OAKLEY: I should very much like to be able to answer that question

DR. KEMBALL PRICE: I should like to ask if people have had experience of coronary thrombosis following starting priscol treatment for peripheral vascular disease particularly in the lower limbs Because I have seen it occur on five occasions within a week of starting the drug which seems more than coincidental

DR GOODWIN: No I have never seen it It is an obvious hazard particularly if you give large doses by injection

CHAIRMAN: When you say it s an obvious hazard do you mean theoretical or because this is common experience

DR GOODWIN: It has been reported and I think it s reasonable theoretically as well

DEMONSTRATIONS

RADIOLOGICAL INVESTIGATION OF ACUTE STROKE

J W D BULL

See text page 76

BLOOD COAGULATION IN ISCHAEMIC HEART DISEASE

LAWSON McDONALD

Coagulation of the blood is shown to be increased in patients with ischaemic heart disease compared with normal subjects These changes become particularly marked during the acute phases of the disease The importance of these findings in the natural history and treatment of ischaemic heart disease is demonstrated

R E F E R E N C E S

McDonald L and Edgill M (1957) Lancet ii 457

McDonald L and Edgill M (1958) ibid i 996

McDonald L and Edgill M (1959) ibid i 1115

MICROSCOPICAL APPEARANCES OF ARTIFICIAL THROMBI PRODUCED BY A MODIFICATION OF CHANDLER'S TECHNIQUE

J C F POOLE

A closed circular loop of plastic tubing is partly filled with blood and mounted on a rotating turntable so that the blood is made to flow continuously round the loop Under these circumstances the blood does not clot at all in the ordinary sense Instead a small solid body appears just behind the advancing edge of the column of blood and floats round for an indefinite period Such bodies have a histological structure resembling a natural thrombus The photomicrographs show the structure and development of these artificial thrombi under a variety of conditions

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